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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/715, 14/54, 16/24, 16/28, G01N 33/566

A1

(11) International Publication Number: **WO 99/40195**

(43) International Publication Date: 12 August 1999 (12.08.99)

(21) International Application Number: PCT/US99/02600

(22) International Filing Date: 5 February 1999 (05.02.99)

(30) Priority Data:

60/073,941	6 February 1998 (06.02.98)	US
09/078,194	13 May 1998 (13.05.98)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract

Nucleic acids encoding mammalian, e.g., primate or rodent receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.

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MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including morphogenesis or immune system function. In particular, it provides nucleic acids, proteins, and antibodies which regulate development and/or the immune system. Various subunits of cytokine receptors, and the matching of subunits in a functional complex are described. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host. See, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.) vols. 1-3, CSH Press, NY.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes,

macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. See, e.g., Paul (ed. 1996) Fundamental Immunology 3d ed., Raven Press, New York; and Thomson (ed. 1994) The Cytokine Handbook 2d ed., Academic Press, San Diego. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

Another important cell lineage is the mast cell (which has not been positively identified in all mammalian species), which is a granule-containing connective tissue cell located proximal to capillaries throughout the body. These cells are found in especially

high concentrations in the lungs, skin, and gastrointestinal and genitourinary tracts. Mast cells play a central role in allergy-related disorders, particularly anaphylaxis as follows: when selected antigens crosslink one class of immunoglobulins bound to receptors on the mast cell surface, the mast cell degranulates and releases mediators, e.g., histamine, serotonin, heparin, and prostaglandins, which cause allergic reactions, e.g., anaphylaxis.

Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

Various growth and regulatory factors exist which modulate morphogenetic development. This includes, e.g., the Toll ligands, which signal through binding to receptors which share structural, and mechanistic, features characteristic of the IL-1 receptors. See, e.g., Lemaitre, et al. (1996) Cell 86:973-983; and Belvin and Anderson (1996) Ann. Rev. Cell & Devel. Biol. 12:393-416. Other receptors for cytokines are also known. Often, there are at least two critical subunits in the functional receptor. See, e.g., Gonda and D'Andrea (1997) Blood 89:355-369; Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007; Drachman and Kaushansky (1995) Curr. Opin. Hematol. 2:22-28; Theze (1994) Eur. Cytokine Netw. 5:353-368; and Lemmon and Schlessinger (1994) Trends Biochem. Sci. 19:459-463.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their receptors, including ones similar to lymphokines, should contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or indirectly involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic

cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present invention provides new receptors for ligands exhibiting similarity to cytokine like compositions and related compounds, and methods for their use.

SUMMARY OF THE INVENTION

The present invention is directed to a novel receptor related to cytokine receptors, e.g., primate or rodent, cytokine receptor like molecular structures, designated DNAX Cytokine Receptor Subunit 1 (DCRS1), and their biological activities. The matching of subunits in a functional receptor, and ligand identification are described. It includes nucleic acids coding for the combinations of polypeptides themselves and methods for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

In certain embodiments, the invention provides a composition of matter selected from the group of: a substantially pure or recombinant DCRS1 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 13 or 4 or 15; a natural sequence DCRS1 comprising SEQ ID NO: 13 or 4 or 15; and a fusion protein comprising DCRS1 sequence. Preferably, the substantially pure or isolated protein comprises a segment exhibiting sequence identity to a corresponding portion of a DCRS1, wherein: the homology is at least about 90% identity and the portion is at least about 9 amino acids; the homology is at least about 80% identity and the portion is at least about 17 amino acids; or the homology is at least about 70% identity and the portion is at least about 25 amino acids. In specific embodiments, the composition of matter is DCRS1, which comprises a mature sequence of

Table 1; or exhibits a non-glycosylated DCRS1; or the composition of matter may be a protein or peptide which: is from a warm blooded animal selected from a mammal, including a primate or rodent, such as a human or mouse; comprises at least one polypeptide segment of SEQ ID NO: 13 or 4 or 15; exhibits a plurality of portions exhibiting said identity; is a natural allelic variant of DCRS1; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate or rodent DCRS1; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a primate or rodent DCRS1; is glycosylated; has a molecular weight of at least 100 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Other embodiments include a composition comprising: a sterile DCRS1 protein or peptide; or the DCRS1 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

In certain fusion protein embodiments, the invention provides a fusion protein comprising: mature protein sequence of Table 1; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another receptor protein.

Various kit embodiments include a kit comprising a DCRS1 protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include those comprising an antigen binding site from an antibody, which specifically binds to a natural DCRS1 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding

compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 1; is raised against a mature DCRS1; is raised to a purified human or mouse DCRS1; is immunoselected; is a polyclonal antibody; binds to a denatured DCRS1; exhibits a Kd to antigen of at least 30 μM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. A binding composition kit often comprises the binding compound, and: a compartment comprising said binding compound; and/or instructions for use or disposal of reagents in the kit. Often the kit is capable of making a qualitative or quantitative analysis.

Other compositions include a composition comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a DCRS1 protein or peptide or fusion protein, wherein: the DCRS1 is from a mammal; or the nucleic acid: encodes an antigenic peptide sequence of Table 1; encodes a plurality of antigenic peptide sequences of Table 1; exhibits at least about 80% identity to a natural cDNA encoding said segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding said DCRS1; or is a PCR primer, PCR product, or mutagenesis primer. A cell, tissue, or organ comprising such a recombinant nucleic acid is also provided. Preferably, the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an

insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Kits are provided comprising such nucleic acids, and: a compartment comprising said nucleic acid; a compartment further comprising a primate or rodent DCRS1 protein or polypeptide; and/or instructions for use or disposal of reagents in the kit. Often, the kit is capable of making a qualitative or quantitative analysis.

Other embodiments include a nucleic acid which: hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 12 or 3 or 14; or exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DCRS1. Preferably, such nucleic acid will have such properties, wherein: wash conditions are at 45° C and/or 500 mM salt; or the identity is at least 90% and/or the stretch is at least 55 nucleotides.

More preferably, the wash conditions are at 55° C and/or 150 mM salt; or the identity is at least 95% and/or the stretch is at least 75 nucleotides.

The invention also provides a method of modulating physiology or development of a cell or tissue culture cells comprising contacting the cell with an agonist or antagonist of a mammalian, e.g., primate or rodent DCRS1. It also provides cells cotransfected with a nucleic acid encoding DCRS1 and another cytokine receptor subunit, e.g., DSRS1. This will allow pairing of subunits to determine the physiological receptor pairs for various cytokine ligands.

The present invention provides various compositions, e.g., comprising both a DSRS1 protein and an isolated or recombinant DCRS1 protein; both an isolated or recombinant DSRS1 protein and a DCRS1 protein; or both a substantially pure or recombinant IL-B30 protein and a DCRS1 protein. In certain embodiments, the DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11; the DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or the IL-B30 has sequence of mature SEQ ID NO: 17 or 19. In other embodiments, at least one of the proteins: is

unglycosylated; is made with synthetic methods; has a detectable label; is attached to a solid substrate; or is conjugated to another chemical moiety.

In other forms, the invention provides a composition comprising: a substantially pure DCRS1 protein and: a DSRS1 protein or an IL-B30 cytokine protein; or a DCRS1 protein and a substantially pure: DSRS1 protein or IL-B30 cytokine protein. Preferred forms combining the DCRS1 and the DSRS1 proteins are those where the proteins combine to bind IL-B30 with high affinity. Yet other forms include sterile compositions, as described.

Kit embodiments include such compositions combined with: a compartment comprising two or more of the proteins; a compartment comprising a soluble receptor alpha subunit; a compartment comprising an IL-B30 cytokine protein; or instructions for use or disposal of reagents in the kit.

Binding composition embodiments include those comprising the antigen binding sites from antibodies, which antibodies bind to an epitope found on a composition described above, but not on separate proteins thereof. Various embodiments include where: the DCRS1 is: a primate protein, a purified human or mouse DCRS1, or a mature polypeptide of Table 1; the DSRS1 is: a primate protein, a purified human or mouse DSRS1, or a mature polypeptide of Table 4; or the IL-B30 is: a primate protein, a purified human or mouse IL-B30, or a mature polypeptide of Table 6. Other embodiments include those where the binding composition: is in a container; is an Fv, Fab, or Fab2 fragment; is conjugated to another chemical moiety; is immunoselected; is a polyclonal antibody; exhibits a Kd to antigen of at least 30 μM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label.

Kit embodiments which comprise the binding compositions further include, e.g., a compartment

comprising the binding composition; a compartment comprising the DCRS1, DSRS1, or IL-B30 protein; or instructions for use or disposal of reagents in the kit.

Certain nucleic acid composition are provided, e.g., an isolated or recombinant nucleic acid encoding both: a DSRS1 protein and a DCRS1 protein; a DSRS1 protein and an IL-B30 protein; or a DCRS1 protein and an IL-B30 protein. Preferred embodiments are those nucleic acids which encode both a DCRS1 protein and a DSRS1 protein; or both a DSRS1 protein and an IL-B30, e.g., in a fusion protein. Other preferred embodiments are those nucleic acids which are expression vectors. Preferably, the DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11; the DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or the IL-B30 has sequence of mature SEQ ID NO: 17 or 19. Specific embodiments are those comprising the coding portion of: SEQ ID NO: 8 or 10; SEQ ID NO: 12 or 14; or SEQ ID NO: 16 or 18.

Transformed cells with the nucleic acids are provided, including where the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Various methods are also provided, e.g., a method of producing a receptor complex, comprising culturing a described transformed cell of in an environment resulting in expression of the DCRS1 and the DSRS1 proteins, thereby forming the receptor complex; or of screening for ligands for a receptor complex comprising the DCRS1 and the DSRS1 proteins, comprising screening a library of compounds for binding to the described cell.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. General

The present invention provides the amino acid sequence and DNA sequence of mammalian, herein primate, cytokine receptor-like subunit molecules, this one

designated DNAX Cytokine Receptor Subunit 1 (DCRS1) having particular defined properties, both structural and biological. Various cDNAs encoding these molecules were obtained from primate, e.g., human, cDNA sequence libraries. Other primate or other mammalian counterparts would also be desired.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

Partial nucleotide (SEQ ID NO: 1) and corresponding amino acid sequence (SEQ ID NO: 2) of a human DCRS1 coding segment is shown in Table 1, with supplementary sequence provided in SEQ ID NO: 12 and 13. Partial mouse sequence is provided (SEQ ID NO: 3 and 4), with supplementary sequence in SEQ ID NO: 14 and 15.

Table 1: Partial nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS1). Primate, e.g., human embodiment (see SEQ ID NO: 1 and 2).

```
gtc tgg ccc ccc gtc ttc gtg aac cta gaa acc caa atg aag cca aac   48
Val Trp Pro Pro Val Phe Val Asn Leu Glu Thr Gln Met Lys Pro Asn
 1               5                  10                  15

gcc ccc cgg ctg ggc cct gac gtg gac ttt tcc gag gat gac ccc ctg   96
Ala Pro Arg Leu Gly Pro Asp Val Asp Phe Ser Glu Asp Asp Pro Leu
            20                  25                  30

gag gcc act gtc cat tgg gcc cca cct aca tgg cca tct cat aaa gtt   144
Glu Ala Thr Val His Trp Ala Pro Pro Thr Trp Pro Ser His Lys Val
        35                  40                  45

ctg atc tgc cag ttc cac tac cga aga tgt cag gag gcg gcc tgg acc   192
Leu Ile Cys Gln Phe His Tyr Arg Arg Cys Gln Glu Ala Ala Trp Thr
    50                  55                  60

ctg ctg gaa ccg gag ctg aag acc ata ccc ctg acc cct gtt gag atc   240
Leu Leu Glu Pro Glu Leu Lys Thr Ile Pro Leu Thr Pro Val Glu Ile
65                  70                  75                  80
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caa gat ttg gag cta gcc act ggc tac aaa gtg tat ggc cgc tgc cgg   288
Gln Asp Leu Glu Leu Ala Thr Gly Tyr Lys Val Tyr Gly Arg Cys Arg
                85                  90                  95

atg gag aaa gaa gag gat ttg tgg ggc gag tgg agc ccc att ttg tcc   336
Met Glu Lys Glu Glu Asp Leu Trp Gly Glu Trp Ser Pro Ile Leu Ser
            100                 105                 110

ttc cag aca ccg cct tct gct cca aaa gat gtg tgg gta tca ggg aac   384
Phe Gln Thr Pro Pro Ser Ala Pro Lys Asp Val Trp Val Ser Gly Asn
        115                 120                 125

ctc tgt ggg acg cct gga gga gag gaa cct ttg ctt cta tgg aag gcc   432
Leu Cys Gly Thr Pro Gly Gly Glu Glu Pro Leu Leu Leu Trp Lys Ala
    130                 135                 140

cca ggg ccc tgt gtg cag gtg agc tac aaa gtc tgg ttc tgg gtt gga   480
Pro Gly Pro Cys Val Gln Val Ser Tyr Lys Val Trp Phe Trp Val Gly
145                 150                 155                 160

ggt cgt gag ctg agt cca gaa gga att acc tgc tgc tgc tcc cta att   528
Gly Arg Glu Leu Ser Pro Glu Gly Ile Thr Cys Cys Cys Ser Leu Ile
                165                 170                 175

ccc agt ggg gcg gag tgg gcc agg gtg tcc gct gtc aac gcc aca agc   576
Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr Ser
            180                 185                 190

tgg gag cct ctc acc aac ctc tct ttg gtc tgc ttg gat tca gcc tct   624
Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala Ser
        195                 200                 205

gcc ccc cgt agc gtg gca gtc agc agc atc gct ggg agc acg gag cta   672
Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu Leu
    210                 215                 220

ctg gtg acc tgg caa ccg ggg cct ggg gaa cca ctg gag cat gta atg   720
Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val Met
225                 230                 235                 240

gac tgg gct cga gat ggg gac ccc ctg gag aaa ctc aac tgg gtc cgg   768
Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val Arg
                245                 250                 255

ctt ccc cct ggg aac ctc agt gct ctg tta cca ggg aat ttc act gtc   816
Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr Val
            260                 265                 270

ggg gtc ccc tat cga atc act gtg acc gca gtc tct gct tca ggc ttg   864
Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly Leu
        275                 280                 285

gcc tct gca tcc tcc gtc tgg ggg ttc agg gag gaa tta gca ccc cta   912
Ala Ser Ala Ser Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro Leu
    290                 295                 300

gtg ggg cca acg ctt tgg cga ctc caa gat gcc cct cca ggg acc ccc   960
Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr Pro
305                 310                 315                 320
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gcc ata gcg tgg gga gag gtc cca agg cac cag ctt cga ggc cac ctc   1008
Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His Leu
                325                 330                 335

acc cac tac acc ttg tgt gca cag agt gga acc agc ccc tcc gtc tgc   1056
Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val Cys
            340                 345                 350

atg aat gtg agt ggc aac aca cag agt gtc acc ctg cct gac ctt cct   1104
Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu Pro
        355                 360                 365

tgg ggt ccc tgt gag ctg tgg gtg aca gca tct acc atc gct gga cag   1152
Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly Gln
    370                 375                 380

ggc cct cct ggt ccc atc ctc cgg ctt cat cta cca gat aac acc ctg   1200
Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr Leu
385                 390                 395                 400

agg tgg aaa gtt ctg ccg ggc atc cta ttc ttg tgg ggc ttg ttc ctg   1248
Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe Leu
                405                 410                 415

ttg ggg tgt ggc ctg agc ctg gcc acc tct gga agg tgc tac cac cta   1296
Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His Leu
            420                 425                 430

agg cac aaa gtg ctg ccc cgc tgg gtc tgg gag aaa gtt cct gat cct   1344
Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp Pro
        435                 440                 445

gcc aac agc agt tca ggc cag ccc cac atg gag caa gta cct gag gcc   1392
Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu Ala
    450                 455                 460

cag ccc ctt ggg gac ttg ccc atc ctg gaa gtg gag gag atg gag ccc   1440
Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu Pro
465                 470                 475                 480

ccg ccg gtt atg gag tcc tcc cag ccc gcc cag gcc acc gcc ccg ctt   1488
Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro Leu
                485                 490                 495

gac tct ggg tat gag aag cac ttc ctg ccc aca cct gag gag ctg ggc   1536
Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu Gly
            500                 505                 510

ctt ctg ggg ccc ccc agg cca cag gtt ctg gcc tgaaccacac gtctggctgg 1589
Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala
        515                 520

gggctgccag ccaggctaga gggatgctca tgcaggttgc accccagtcc tggattagcc 1649

ctcttgatgg atgaagacac tgaggactca gagaggctga gtcacttacc tgaggacacc 1709

cagccaggca gagctgggat tgaaggaccc ctatagagaa gggcttggcc cccatgggga 1769

agacacggat ggaaggtgga gcaaaggaaa atacatgaaa ttgagagtgg cagctgcctg 1829

ccaaaatctg ttccgctgta acagaactga atttggaccc cagcacagtg gctcacgcct 1889
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gtaatcccag cactttggca ggccaaggtg gaaggatcac ttagagctag gagtttgaga 1949

ccagcctggg caatatagca agacccctca ctacaaaaat aaaacatcaa aaacaaaaac 2009

aattagctgg gcatgatggc acacacctgt agtccgagcc acttgggagg ctgaggtggg 2069

aggatcggtt gagcccagga gtttgaagct gcagggacct ctgattgcac cactgcactc 2129

caggctgggt aacagaatga gaccttatyt caaaaataaa caaactaatw aaaarmaaaa 2189

aaaaaaamwm raraaaaaaa aaaa 2213

Partial "downstream" sequences of rodent, e.g., mouse, embodiment of DCRS1 (SEQ ID NO: 3 and 4):

aaa gga ggg gtc ccc tat cga att aca gtg act gca gta tac tct gga 48
Lys Gly Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Tyr Ser Gly
1 5 10 15

gga tta gct gct gca ccc tca gtt tgg gga ttc aga gag gag tta gta 96
Gly Leu Ala Ala Ala Pro Ser Val Trp Gly Phe Arg Glu Glu Leu Val
20 25 30

ccc ctt gct ggg cca gca gtt tgg cga ctt cca gat gac ccc cca ggg 144
Pro Leu Ala Gly Pro Ala Val Trp Arg Leu Pro Asp Asp Pro Pro Gly
35 40 45

aca cct gtt gta gcc tgg gga gaa gta cca aga cac cag ctc aga ggc 192
Thr Pro Val Val Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly
50 55 60

cag gct act cac tac acc ttc tgc ata cag agc aga ggc ctc tcc act 240
Gln Ala Thr His Tyr Thr Phe Cys Ile Gln Ser Arg Gly Leu Ser Thr
65 70 75 80

gtc tgc agg aac gtg agc agt caa acc cag act gcc act ctg ccc aac 288
Val Cys Arg Asn Val Ser Ser Gln Thr Gln Thr Ala Thr Leu Pro Asn
85 90 95

ctt cac tcg ggt tcc ttc aag ctg tgg gtg acg gtg tcc acc gtt gca 336
Leu His Ser Gly Ser Phe Lys Leu Trp Val Thr Val Ser Thr Val Ala
100 105 110

gga cag ggc cca cct ggt ccc gac ctt tca ctt cac cta cca gat aat 384
Gly Gln Gly Pro Pro Gly Pro Asp Leu Ser Leu His Leu Pro Asp Asn
115 120 125

agg atc agg tgg aaa gct ctg ccc tgg ttt ctg tcc ctg tgg ggt ttg 432
Arg Ile Arg Trp Lys Ala Leu Pro Trp Phe Leu Ser Leu Trp Gly Leu
130 135 140

ctt ctg atg ggc tgt ggc ctg agc ctg gcc agt acc agg tgc cta cag 480
Leu Leu Met Gly Cys Gly Leu Ser Leu Ala Ser Thr Arg Cys Leu Gln
145 150 155 160

gcc agg tgc tta cac tgg cga cac aag ttg ctt ccc cag tgg atc tgg 528
Ala Arg Cys Leu His Trp Arg His Lys Leu Leu Pro Gln Trp Ile Trp
165 170 175

```
gag agg gtt cct gat cct gcc aac agc aat tct ggg caa cct tac atc   576
Glu Arg Val Pro Asp Pro Ala Asn Ser Asn Ser Gly Gln Pro Tyr Ile
            180                 185                 190

aag gag gtg agc ctg ccc caa ccg ccc aag gac gga ccc atc ctg gag   624
Lys Glu Val Ser Leu Pro Gln Pro Pro Lys Asp Gly Pro Ile Leu Glu
        195                 200                 205

gtg gag gaa gtg gag cta cag cct gtt gtg gag tcc cct aaa gcc tct   672
Val Glu Glu Val Glu Leu Gln Pro Val Val Glu Ser Pro Lys Ala Ser
    210                 215                 220

gcc ccg att tac tct ggg tat gag aaa cac ttc ctg ccc aca cca gag   720
Ala Pro Ile Tyr Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu
225                 230                 235                 240

gag ctg ggc ctt cta gtc tgatctgctt acggctaggg gctgtacccc          768
Glu Leu Gly Leu Leu Val
                245

tatcttgggc tagacgtttt tgtattttta gatttttgag acaggatctc actatggctg 828

gcctggaact tgatataaca accaggctgg cctggaactc accaagactc acctggtttt 888

gccttccaag gactgagaag aaatgagtgt gccgcctccc gcccaaccag cttttgcttt 948

ccttgcctct gggtcttggg catctgtttg ttactgcaga agaatcagtg agctcacagc 1008

ctcgaacttg tgatcctccc tgctgcagca tccccagagc tgggattaca ggtgtgcgtc 1068
acttcatcga gtcataactt ttgattctag tgagaataac taccaggcag gctatgaggt 1128

ggtgactcga aagacacatt caaggaccta aagtggttaa gagcctgtgt tttcttgcag 1188

tagaccaaag tttggttccc tgcccttgca aaggacacac gttcagtttc cagcacccac 1248

agggcagttc agaatcacct gtaactccag gtccaaggaa tccaatgccc tcttctggct 1308

tctgtgagcc ccgcacacac atggttactt atgcaccgaa aaacacacgc ataaaataaa 1368

aataaataaa taaataaaaa taaattaata aataatcttt tttttcttaa aaaaaaaaaa 1428

aaa                                                               1431
```

supplementary primate, e.g., human, DCRS1 sequence (SEQ ID NO: 12 and 13):

```
atg cgg gga ggc agg ggc gcc cct ttc tgg ctg tgg ccg ctg ccc aag   48
Met Arg Gly Gly Arg Gly Ala Pro Phe Trp Leu Trp Pro Leu Pro Lys
  1               5                  10                  15

ctg gcg ctg ctg cct ctg ttg tgg gtg ctt ttc cag cgg acg cgt ccc   96
Leu Ala Leu Leu Pro Leu Leu Trp Val Leu Phe Gln Arg Thr Arg Pro
            20                  25                  30

cag ggc agc gcc ggg cca ctg cag tgc tac gga gtt gga ccc ttg ggc  144
Gln Gly Ser Ala Gly Pro Leu Gln Cys Tyr Gly Val Gly Pro Leu Gly
        35                  40                  45
```

```
gac ttg aac tgc tcg tgg gag cct ctt ggg gac ctg gga gcc ccc tcc   192
Asp Leu Asn Cys Ser Trp Glu Pro Leu Gly Asp Leu Gly Ala Pro Ser
     50                  55                  60

gag tta cac ctc cag agc caa aag tac cgt tcc aac aaa acc cag act   240
Glu Leu His Leu Gln Ser Gln Lys Tyr Arg Ser Asn Lys Thr Gln Thr
 65                  70                  75                  80

gtg gca gtg gca gcc gga cgg agc tgg gtg gcc att cct cgg gaa cag   288
Val Ala Val Ala Ala Gly Arg Ser Trp Val Ala Ile Pro Arg Glu Gln
                 85                  90                  95

ctc acc atg tct gac aaa ctc ctt gtc tgg ggc ayt aag gca ggc cag   336
Leu Thr Met Ser Asp Lys Leu Leu Val Trp Gly Xaa Lys Ala Gly Gln
            100                 105                 110

cct ctc tgg ccc ccc gtc ttc gtg aac cta gaa acc caa atg aag cca   384
Pro Leu Trp Pro Pro Val Phe Val Asn Leu Glu Thr Gln Met Lys Pro
        115                 120                 125

aac gcc ccc cgg ctg ggc cct gac gtg gac ttt tcc gag gat gac ccc   432
Asn Ala Pro Arg Leu Gly Pro Asp Val Asp Phe Ser Glu Asp Asp Pro
    130                 135                 140

ctg gag gcc act gtc cat tgg gcc cca cct aca tgg cca tct cat aaa   480
Leu Glu Ala Thr Val His Trp Ala Pro Pro Thr Trp Pro Ser His Lys
145                 150                 155                 160

gtt ctg atc tgc cag ttc cac tac cga aga tgt cag gag gcg gcc tgg   528
Val Leu Ile Cys Gln Phe His Tyr Arg Arg Cys Gln Glu Ala Ala Trp
                165                 170                 175

acc ctg ctg gaa ccg gag ctg aag acc ata ccc ctg acc cct gtt gag   576
Thr Leu Leu Glu Pro Glu Leu Lys Thr Ile Pro Leu Thr Pro Val Glu
            180                 185                 190

atc caa gat ttg gag cta gcc act ggc tac aaa gtg tat ggc cgc tgc   624
Ile Gln Asp Leu Glu Leu Ala Thr Gly Tyr Lys Val Tyr Gly Arg Cys
        195                 200                 205

cgg atg gag aaa gaa gag gat ttg tgg ggc gag tgg agc ccc att ttg   672
Arg Met Glu Lys Glu Glu Asp Leu Trp Gly Glu Trp Ser Pro Ile Leu
    210                 215                 220

tcc ttc cag aca ccg cct tct gct cca aaa gat gtg tgg gta tca ggg   720
Ser Phe Gln Thr Pro Pro Ser Ala Pro Lys Asp Val Trp Val Ser Gly
225                 230                 235                 240

aac ctc tgt ggg acg cct gga gga gag gaa cct ttg ctt cta tgg aag   768
Asn Leu Cys Gly Thr Pro Gly Gly Glu Glu Pro Leu Leu Leu Trp Lys
                245                 250                 255

gcc cca ggg ccc tgt gtg cag gtg agc tac aaa gtc tgg ttc tgg gtt   816
Ala Pro Gly Pro Cys Val Gln Val Ser Tyr Lys Val Trp Phe Trp Val
            260                 265                 270

gga ggt cgt gag ctg agt cca gaa gga att acc tgc tgc tgc tcc cta   864
Gly Gly Arg Glu Leu Ser Pro Glu Gly Ile Thr Cys Cys Cys Ser Leu
        275                 280                 285
```

```
att ccc agt ggg gcg gag tgg gcc agg gtg tcc gct gtc aac gcc aca   912
Ile Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr
    290                 295                 300

agc tgg gag cct ctc acc aac ctc tct ttg gtc tgc ttg gat tca gcc   960
Ser Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala
305                 310                 315                 320

tct gcc ccc cgt agc gtg gca gtc agc agc atc gct ggg agc acg gag   1008
Ser Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu
                325                 330                 335

cta ctg gtg acc tgg caa ccg ggg cct ggg gaa cca ctg gag cat gta   1056
Leu Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val
            340                 345                 350

atg gac tgg gct cga gat ggg gac ccc ctg gag aaa ctc aac tgg gtc   1104
Met Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val
        355                 360                 365

cgg ctt ccc cct ggg aac ctc agt gct ctg tta cca ggg aat ttc act   1152
Arg Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr
    370                 375                 380

gtc ggg gtc ccc tat cga atc act gtg acc gca gtc tct gct tca ggc   1200
Val Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly
385                 390                 395                 400

ttg gcc tct gca tcc tcc gtc tgg ggg ttc agg gag gaa tta gca ccc   1248
Leu Ala Ser Ala Ser Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro
                405                 410                 415

cta gtg ggg cca acg ctt tgg cga ctc caa gat gcc cct cca ggg acc   1296
Leu Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr
            420                 425                 430

ccc gcc ata gcg tgg gga gag gtc cca agg cac cag ctt cga ggc cac   1344
Pro Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His
        435                 440                 445

ctc acc cac tac acc ttg tgt gca cag agt gga acc agc ccc tcc gtc   1392
Leu Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val
    450                 455                 460

tgc atg aat gtg agt ggc aac aca cag agt gtc acc ctg cct gac ctt   1440
Cys Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu
465                 470                 475                 480

cct tgg ggt ccc tgt gag ctg tgg gtg aca gca tct acc atc gct gga   1488
Pro Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly
                485                 490                 495

cag ggc cct cct ggt ccc atc ctc cgg ctt cat cta cca gat aac acc   1536
Gln Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr
            500                 505                 510

ctg agg tgg aaa gtt ctg ccg ggc atc cta ttc ttg tgg ggc ttg ttc   1584
Leu Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe
        515                 520                 525
```

```
ctg ttg ggg tgt ggc ctg agc ctg gcc acc tct gga agg tgc tac cac   1632
Leu Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His
    530                 535                 540

cta agg cac aaa gtg ctg ccc cgc tgg gtc tgg gag aaa gtt cct gat   1680
Leu Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp
545                 550                 555                 560

cct gcc aac agc agt tca ggc cag ccc cac atg gag caa gta cct gag   1728
Pro Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu
                565                 570                 575

gcc cag ccc ctt ggg gac ttg ccc atc ctg gaa gtg gag gag atg gag   1776
Ala Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu
            580                 585                 590

ccc ccg ccg gtt atg gag tcc tcc cag ccc gcc cag gcc acc gcc ccg   1824
Pro Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro
        595                 600                 605

ctt gac tct ggg tat gag aag cac ttc ctg ccc aca cct gag gag ctg   1872
Leu Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu
    610                 615                 620

ggc ctt ctg ggg ccc ccc agg cca cag gtt ctg gcc tga               1911
Gly Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala
625                 630                 635

MRGGRGAPFW LWPLPKLALL PLLWVLFQRT RPQGSAGPLQ CYGVGPLGDL NCSWEPLGDL
GAPSELHLQS QKYRSNKTQT VAVAAGRSWV AIPREQLTMS DKLLVWG.KA GQPLWPPVFV
NLETQMKPNA PRLGPDVDFS EDDPLEATVH WAPPTWPSHK VLICQFHYRR CQEAAWTLLE
PELKTIPLTP VEIQDLELAT GYKVYGRCRM EKEEDLWGEW SPILSFQTPP SAPKDVWVSG
NLCGTPGGEE PLLLWKAPGP CVQVSYKVWF WVGGRELSPE GITCCCSLIP SGAEWARVSA
VNATSWEPLT NLSLVCLDSA SAPRSVAVSS IAGSTELLVT WQPGPGEPLE HVMDWARDGD
PLEKLNWVRL PPGNLSALLP GNFTVGVPYR ITVTAVSASG LASASSVWGF REELAPLVGP
TLWRLQDAPP GTPAIAWGEV PRHQLRGHLT HYTLCAQSGT SPSVCMNVSG NTQSVTLPDL
PWGPCELWVT ASTIAGQGPP GPILRLHLPD NTLRWKVLPG ILFLWGLFLL GCGLSLATSG
RCYHLRHKVL PRWVWEKVPD PANSSSGQPH MEQVPEAQPL GDLPILEVEE MEPPPVMESS
QPAQATAPLD SGYEKHFLPT PEELGLLGPP RPQVLA
```

supplementary partial "upstream" rodent, e.g., mouse, DCRP1 sequences (SEQ ID NO: 14 and 15):

```
ggt aag ccc caa gcc tgg tgg tgt cac ttg tcc ctg gga gcc atg aac   48
Gly Lys Pro Gln Ala Trp Trp Cys His Leu Ser Leu Gly Ala Met Asn
  1               5                  10                  15

cgg ctc ggg ttt gca cgc ctc acg ccg ttg gag ctt ctg ctg tcg ctg   96
Arg Leu Gly Phe Ala Arg Leu Thr Pro Leu Glu Leu Leu Leu Ser Leu
            20                  25                  30

atg tcg ctg ctg ctc ggg acg cgg ccc cac ggc agt cca ggc cca ctg   144
Met Ser Leu Leu Leu Gly Thr Arg Pro His Gly Ser Pro Gly Pro Leu
        35                  40                  45

cag tgc tac agc gtc ggt ccc ctg gga atc ctg aac tgc tcc tgg gaa   192
Gln Cys Tyr Ser Val Gly Pro Leu Gly Ile Leu Asn Cys Ser Trp Glu
    50                  55                  60
```

```
cct ttg ggc gac ctg gag act cca cct gtg ctg tat cac cag agt cag   240
Pro Leu Gly Asp Leu Glu Thr Pro Pro Val Leu Tyr His Gln Ser Gln
 65                  70                  75                  80

aaa tac cat ccc aat aga gtc tgg gag gtg aag gtg cct tcc aaa cag   288
Lys Tyr His Pro Asn Arg Val Trp Glu Val Lys Val Pro Ser Lys Gln
                 85                  90                  95

agt tgg gtg acc att ccc cgg gaa cag ttc acc atg gct gac aaa ctc   336
Ser Trp Val Thr Ile Pro Arg Glu Gln Phe Thr Met Ala Asp Lys Leu
            100                 105                 110

ctc atc tgg ggg aca caa aag gga cgg cct ctg tgg tcc tct gtc tct   384
Leu Ile Trp Gly Thr Gln Lys Gly Arg Pro Leu Trp Ser Ser Val Ser
        115                 120                 125

gtg aac ctg gag acc caa atg aag cca gac aca cct cag atc ttc tct   432
Val Asn Leu Glu Thr Gln Met Lys Pro Asp Thr Pro Gln Ile Phe Ser
    130                 135                 140

caa gtg gat att tct gan                                          450
Gln Val Asp Ile Ser Xaa
145                 150
```

Table 2: Comparison of rodent, e.g., mouse, and primate, e.g., human, DCRS1:

```
mDCRS1   -----MNRLGXARLTPLELLLSLMSLLLGTRPHGSPGPLQCYSVGPLGILNCSWEPLGDL
hDCRS1   MRGGRGAPFWLWPLPKLALLPLLWVLFQRTRPQGSAGPLQCYGVGPLGDLNCSWEPLGDL
                  :    *. * **  *  *:  ***:**.******.***** ***********

mDCRS1   ETPPVLYHQSQKYHPNRVWEVKVPSKQSWVTIPREQFTMADKLLIWGTQKGRPLWSSVSV
hDCRS1   GAPSELHLQSQKYRSNKTQTVAVAAGRSWVAIPREQLTMSDKLLVWGXKAGQPLWPPVFV
          :*. *: * ***:.*:.  * *.: :***:*****:**:****:***: *:***..* *

mDCRS1   NLETQMKPDTPQIFSQVDIS----------------------------------------
hDCRS1   NLETQMKPNAPRLGPDVDFSEDDPLEATVHWAPPTWPSHKVLICQFHYRRCQEAAWTLLE
         * ******::*:: .:**:*

mDCRS1   ------------------------------------------------------------
hDCRS1   PELKTIPLTPVEIQDLELATGYKVYGRCRMEKEEDLWGEWSPILSFQTPPSAPKDVWVSG

mDCRS1   ------------------------------------------------------------
hDCRS1   NLCGTPGGEEPLLLWKAPGPCVQVSYKVWFWVGGRELSPEGITCCCSLIPSGAEWARVSA

mDCRS1   ------------------------------------------------------------
hDCRS1   VNATSWEPLTNLSLVCLDSASAPRSVAVSSIAGSTELLVTWQPGPGEPLEHVMDWARDGD

mDCRS1   ----------------------KGGVPYRITVTAVYSGGLAAAPSVWGFREELVPLAGP
hDCRS1   PLEKLNWVRLPPGNLSALLPGNFTVGVPYRITVTAVSASGLASASSVWGFREELAPLVGP
                               *********** . ***.* ********* ** **
```

```
mDCRS1    AVWRLPDDPPGTPVVAWGEVPRHQLRGQATHYTFCIQSRGLSTVCRNVSSQTQTATLPNL
hDCRS1    TLWRLQDAPPGTPAIAWGEVPRHQLRGHLTHYTLCAQSGTSPSVCMNVSGNTQSVTLPDL
          ..*** * ***** .************. **** * **     .** *** .**. *** *

mDCRS1    HSGSFKLWVTVSTVAGQGPPGPDLSLHLPDNRIRWKALPWFLSLWGLLLMGCGLSLASTR
hDCRS1    PWGPCELWVTASTIAGQGPPGPILRLHLPDNTLRWKVLPGILFLWGLFLLGCGLSLATS-
            *   **** **.******** * ****** .*** **  * **** *.*******..

mDCRS1    CLQARCLHWRHKLLPQWIWERVPDPANSNSGQPYIKEVSLPQPPKDGPILEVEEVELQPV
hDCRS1    ---GRCYHLRHKVLPRWVWEKVPDPANSSSGQPHMEQVPEAQPLGDLPILEVEEMEPPPV
              ** * ***.**.*.**.******* **** . .*   **  * *******.*  **

mDCRS1    VESPK---ASAPIYSGYEKHFLPTPEELGLLV
hDCRS1    MESSQPAQATAPLDSGYEKHFLPTPEELGLLGPPRPQVLA
          .**  .   *.**. *****************
```

Table 3: Alignment of various cytokine receptor subunits. Human gp130 sequence (hgp130) is SEQ ID NO: 5 (see GenBank M57230). Human G-CSF Receptor subunit alpha (hGCSFRa) is SEQ ID NO: 6 (see GenBank X55721). Human IL-12 Receptor subunit beta (hIL12Rb) is SEQ ID NO: 7 (see GenBank U64198). Consensus domain boundaries are described in the text.

```
mIL30Rb           ----------MNRLGXARLTPLELLLSLMSLLLGTR----------
hIL30Rb           ------MRGGRGAPFWLWPLPKLALLPLLWVLFQRTR----------
human_GCSF        -------MARLGNCSLTWAALIILLLPGSLEECGHISVSAPIVHLGDPIT
human_gp13        MLTLQTWVVQALFIFLTTESTGELLDP-----CGYISPESPVVQLHSNFT
human_IL12        MAHTFRGCSLAFMFIITWLLIKAKIDACK--RGDVTVKPSHVILLGSTVN
                                              :

mIL30Rb           --------------------------------------------------
hIL30Rb           --------------------------------------------------
human_GCSF        ASCIIK--QNCSHLDPEPQ--ILWRLGAELQPGGRQQRLSDGTQESIITL
human_gp13        AVCVLK--EKCMDYFHVNANYIVWKTNHFTIPKE-QYTIINRTASSVTFT
human_IL12        ITCSLKPRQGCFHYSRRNK-LILYKFDRRINFHHGHSLNSQVTGLPLG--
                                           :

mIL30Rb           --------------------------------PHGSPGPLQCYSVGPLGI
hIL30Rb           --------------------------------PQGSAGPLQCYGVGPLGD
human_GCSF        PHLNHTQAFLSCCLNWGNSLQILDQVELRAGYPPAIPHNLSCLMNLTTSS
human_gp13        DIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGK-K
human_IL12        -----TTLFVCKLACINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQGT
                                                    .     *.*

mIL30Rb           LNCSWEPLGDLETPPVLYHQSQKYHPN-----RVWEVKVPS-KQSWVTIP
hIL30Rb           LNCSWEPLGDLGAPSELHLQXQKYRSN-----KTQTVAVAA-GRSWVAIP
human_GCSF        LICQWEPGPETHLPTSFTLKSFKSRGNCQTQGDSILDCVPKDGQSHCCIP
human_gp13        MRCEWDGGRETHLETNFTLKS-EWATH-----KFADCKAKRDTPTSCTVD
human_IL12        VACTWERGRDTHLYTEYTLQL-SGPKN---LTWQKQCKDIYCDYLDFGIN
                  : * *:   :    .   : .  :                      :
```

```
mIL30Rb     REQFTMADKLLIWGTQK---GRPLWSSVSVNLETQMKPDTPQIFSQVDIS
hIL30Rb     REQLTMSDKLLVWGTKA---GQPLWPPVFVNLETQMKPNAPRLGPDVDFS
human_GCSF  RKHLLLYQNMGIWVQAENALGTSMSPQLCLDPMDVVKLEPPMLRTMDPSP
human_gp13  YS-TVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSE
human_IL12  LTPESPESNFTAKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQK
                 ::          *        .     ::  .*

mIL30Rb     --------------------------------------------------
hIL30Rb     EDDPLEA---TVHWAPPTWPSHKVLICQF-HYRRCQEAAWTLLEPELKTI
human_GCSF  EAAPPQAGCLQLCWEPWQPGLHINQKCELRHKPQRGEASWALVGPLP--L
human_gp13  ELSSILK----LTWTNPSIKSVIILKYNI-QYRTKDASTWSQIPPEDTAS
human_IL12  ASVSRCT----LYWRDE-----GLVLLNRLRYRPSNSRLWNMVNVTK---

mIL30Rb     --------------------------------------------------
hIL30Rb     PLTPVEIQDLELATGYKVYGRCRMEKEEDLWGEWSPILSFQTPPSAP---
human_GCSF  EALQYELCGLLPATAYTLQIRCIRWPLPGHWSDWSPSLELRTTERAPTVR
human_gp13  TRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKA
human_IL12  AKGRHDLLDLKPFTEYEFQISSKLHLYKGSWSDWSESLRAQTPEEEPTGM

mIL30Rb     --------------------------------------------------
hIL30Rb     KDVWVSG------NLCGTPGGEEPLLLWKAPGPCVQVSYKVWFWVG---G
human_GCSF  LDTWWRQR---QLDPRTVQLFWKPVPLEEDSG-RIQGYVVSWRPSGQ--A
human_gp13  PSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKS---H
human_IL12  LDVWYMKR-HIDYSRQQISLFWKNLSVSEARGKILHYQVTLQELTGGKAM

mIL30Rb     --------------------------------------------------
hIL30Rb     RELSPEGITCCCSLIPSGAEWARVSAVNATSWEPLTNLSLVCLDSASAPR
human_GCSF  GAILPLCNTTELSCTFHLPSEAQEVALVAYNSAGTSRPTPVVFSESRGPA
human_gp13  LQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHP
human_IL12  TQNITGHTSWTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGLLA

mIL30Rb     --------------------------------------------------
hIL30Rb     SVAVSSIAGS-TELLVTWQPGPGEP---LEHVMDWARDGD-PLEKLN--W
human_GCSF  LTRLHAMARDPHSLWVGWEPPNPWP---QGYVIEWGLGPP-SASNSNKTW
human_gp13  VMDLKAFPKD-NMLWVEWTTPRESV---KKYILEWCVLSD-KAPCIT-DW
human_IL12  PRQVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNW

mIL30Rb     ----------------KGGVPYRITVTAVYSGGLAAAPSVWGFREELVP
hIL30Rb     VRLPPG-NLSALLPGNFTVGVPYRITVTAVSASGLASASSVWGFREELAP
human_GCSF  RMEQNGRATGFLLKENIRPFQLYEIIVTPLYQDTMGPSQHVYAYSQEMAP
human_gp13  QQE-DGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPP
human_IL12  LRS-RPYNVSALISENIKSYICYEIRVYALSGD-QGGCSSILGNSKHKAP

mIL30Rb     LAGPAVWRLPDDPPGTPVVAWGEVPRHQLRGQATHYTFCIQ----SRGLS
hIL30Rb     LVGPTLWRLQDAPPGTPAIAWGEVPRHQLRGHLTHYTLCAQ----SGTSP
human_GCSF  SHAP-ELHLKHIGKTWAQLEWVPEPPELGKSPLTHYTIFWT----NAQNQ
human_gp13  SKGP-TVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYR----TIIGN
human_IL12  LSGP-HINAITEEKGSILISWNSIPVQEQMGCLLHYRIYWKERDSNSQPQ
```

```
mIL30Rb      TVCRNVSSQTQTATLPNLHSGSFKLWVTVSTVAGQGPPGPDLSLHLPDNR
hIL30Rb      SVCMNVSGNTQSVTLPDLPWGPCELWVTASTIAGQGPPGPILRLHLPDNT
human_GCSF   SFSAILNASSRGFVLHGL--EPASLYHIHLMAASQAGATNSTVLTLMTLT
human_gp13   ETAVNVDSSHTEYTLSSL--TSDTLYMVRMAAYTDEGGKDGPEFTFTTPK
human_IL12   LCEIPYRVSQNSHPINSL--QPRVTYVLWMTALTAAGESSHGNEREFCLQ

mIL30Rb      IRWKALPWFLSLWGLLLMGCGLSLASTRCLQARCLHWRHKLLPQWIWER-
hIL30Rb      LRWKVLPGILFLWGLFLLGCGLSLATS----GRCYHLRHKVLPRWVWEK-
human_GCSF   PEGSELHIILGLFGLLLLLTCLCGTAW----LCCSPNR----KNPLWPS-
human_gp13   FAQGEIEAIVVPVCLAFLLTTLLG------VLFCFNKR-DLIKKHIWPN-
human_IL12   GKANWMAFVAPSICIAIIMVGIFSTHY----FQQKVFVLLAALRPQWCSR

mIL30Rb      -VPDPANSNSG-------QPYIKEVS----LPQPPKDGP---ILEVEEVE
hIL30Rb      -VPDPANSSSG-------QPHMEQVP----EAQPLGDLP---ILEVEE--
human_GCSF   -VPDPAHSSLGSWVPTIMEEDAFQLPG--LGTPPITKLT---VLEEDE--
human_gp13   -VPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVS---VVEIEAND
human_IL12   EIPDPANSTCAKKYPIAEEKTQLPLDR-LLIDWPTPEDPEPLVISEVLHQ

mIL30Rb      LQPV----------------------------PVVESPK---AS-------
hIL30Rb      MEPP----------------------------PVMESSQPAQAT-------
human_GCSF   KKPVPWESHNSSET--CGLPTLVQTYVLQGDPRAVSTQPQSQSG----TS
human_gp13   KKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESS
human_IL12   VTPVFRHPPCSNWPQREKGIQGHQASEKDMMHSASSPPPPRALQAE---S

mIL30Rb      ----------APIYSG------------YEKHFLPTP-------------
hIL30Rb      ----------APLDSG------------YEKHFLPTP-------------
human_GCSF   DQVLYGQLLGSPTSPGPGHYLRCDSTQPLLAGLTPSPKSYENLW----FQ
human_gp13   QNTSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVD
human_IL12   RQLVDLYKVLESRGSDPKPENPACPWTVLPAGDLPTHDGYLP------SN

mIL30Rb      -EELGLLV-----------------------------------------
hIL30Rb      -EELGLLGPPRP-QVLA-------------------------------
human_GCSF   ASPLGTLVTPAP-SQEDDCVFG---P-LLNFPLLQGIRVHGMEALGSF--
human_gp13   HVDGGDGILPRQQYFKQNCSQHESSPDISHFERSKQVSSVNEEDFVRLKQ
human_IL12   IDDLPSHEAPLADSLEELEPQHISLSVFPSSSLHPLTFSCGDKLTLDQLK

mIL30Rb      ------------------------------------------------
hIL30Rb      ------------------------------------------------
human_GCSF   ------------------------------------------------
human_gp13   QISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEAATDEG
human_IL12   MRCDSLML--------------------------------------------

mIL30Rb      ----------------
hIL30Rb      ----------------
human_GCSF   ----------------
human_gp13   MPKSYLPQTVRQGGYMPQ
human_IL12   ----------------
```

Table 4: Sequences of mammalian DNAX Soluble Receptor Subunit 1 (DSRS1). Primate, e.g., human, nucleotide and polypeptide sequences (SEQ ID NO: 8 and 9; note WSEWS motif at 327-331):

```
atg ccc gcc ggc cgc cgg ggc ccc gcc gcc caa tcc gcg cgg cgg ccg   48
Met Pro Ala Gly Arg Arg Gly Pro Ala Ala Gln Ser Ala Arg Arg Pro
  1               5                  10                  15

ccg ccg ttg ctg ccc ctg ctg ctg ctg ctc tgc gtc ctc ggg gcg ccg   96
Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Ala Pro
            20                  25                  30

cga gcc gga tca gga gcc cac aca gct gtg atc agt ccc cag gat ccc  144
Arg Ala Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro Gln Asp Pro
        35                  40                  45

acg ctt ctc atc ggc tcc tcc ctg ctg gcc acc tgc tca gtg cac gga  192
Thr Leu Leu Ile Gly Ser Ser Leu Leu Ala Thr Cys Ser Val His Gly
    50                  55                  60

gac cca cca gga gcc acc gcc gag ggc ctc tac tgg acc ctc aac ggg  240
Asp Pro Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly
65                  70                  75                  80

cgc cgc ctg ccc cct gag ctc tcc cgt gta ctc aac gcc tcc acc ttg  288
Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn Ala Ser Thr Leu
                85                  90                  95

gct ctg gcc ctg gcc aac ctc aat ggg tcc agg cag cgg tcg ggg gac  336
Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Arg Ser Gly Asp
            100                 105                 110

aac ctc gtg tgc cac gcc cgt gac ggc agc atc ctg gct ggc tcc tgc  384
Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys
        115                 120                 125

ctc tat gtt ggc ctg ccc cca gag aaa ccc gtc aac atc agc tgc tgg  432
Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn Ile Ser Cys Trp
    130                 135                 140

tcc aag aac atg aag gac ttg acc tgc cgc tgg acg cca ggg gcc cac  480
Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala His
145                 150                 155                 160

ggg gag acc ttc ctc cac acc aac tac tcc ctc aag tac aag ctt agg  528
Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg
                165                 170                 175

tgg tat ggc cag gac aac aca tgt gag gag tac cac aca gtg ggg ccc  576
Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly Pro
            180                 185                 190

cac tcc tgc cac atc ccc aag gac ctg gct ctc ttt acg ccc tat gag  624
His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu
        195                 200                 205

atc tgg gtg gag gcc acc aac cgc ctg ggc tct gcc cgc tcc gat gta  672
Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp Val
    210                 215                 220
```

```
ctc acg ctg gat atc ctg gat gtg gtg acc acg gac ccc ccg ccc gac   720
Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp Pro Pro Pro Asp
225                 230                 235                 240

gtg cac gtg agc cgc gtc ggg ggc ctg gag gac cag ctg agc gtg cgc   768
Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val Arg
                245                 250                 255

tgg gtg tcg cca ccc gcc ctc aag gat ttc ctc ttt caa gcc aaa tac   816
Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr
            260                 265                 270

cag atc cgc tac cga gtg gag gac agt gtg gac tgg aag gtg gtg gac   864
Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val Asp
        275                 280                 285

gat gtg agc aac cag acc tcc tgc cgc ctg gcc ggc ctg aaa ccc ggc   912
Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly
    290                 295                 300

acc gtg tac ttc gtg caa gtg cgc tgc aac ccc ttt ggc atc tat ggc   960
Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly
305                 310                 315                 320

tcc aag aaa gcc ggg atc tgg agt gag tgg agc cac ccc aca gcc gcc  1008
Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala Ala
                325                 330                 335

tcc act ccc cgc agt gag cgc ccg ggc ccg ggc ggc ggg gcg tgc gaa  1056
Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Ala Cys Glu
            340                 345                 350

ccg cgg ggc gga gag ccg agc tcg ggg ccg gtg cgg cgc gag ctc aag  1104
Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu Lys
        355                 360                 365

cag ttc ctg ggc tgg ctc aag aag cac gcg tac tgc tcc aac ctc agc  1152
Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu Ser
    370                 375                 380

ttc cgc ctc tac gac cag tgg cga gcc tgg atg cag aag tcg cac aag  1200
Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His Lys
385                 390                 395                 400

acc cgc aac cag gtc ctg cca gat aag ctg tag                     1233
Thr Arg Asn Gln Val Leu Pro Asp Lys Leu
                405                 410
```

```
MPAGRRGPAA QSARRPPPLL PLLLLLCVLG APRAGSGAHT AVISPQDPTL LIGSSLLATC
SVHGDPPGAT AEGLYWTLNG RRLPPELSRV LNASTLALAL ANLNGSRQRS GDNLVCHARD
GSILAGSCLY VGLPPEKPVN ISCWSKNMKD LTCRWTPGAH GETFLHTNYS LKYKLRWYGQ
DNTCEEYHTV GPHSCHIPKD LALFTPYEIW VEATNRLGSA RSDVLTLDIL DVVTTDPPPD
VHVSRVGGLE DQLSVRWVSP PALKDFLFQA KYQIRYRVED SVDWKVVDDV SNQTSCRLAG
LKPGTVYFVQ VRCNPFGIYG SKKAGIWSEW SHPTAASTPR SERPGPGGGA CEPRGGEPSS
GPVRRELKQP LGWLKKHAYC SNLSFRLYDQ WRAWMQKSHK TRNQVLPDKL
```

Partial rodent, e.g., mouse, nucleotide and polypeptide sequences, note WSEWS motif at 321-325 (SEQ ID NO: 10 and 11):

```
ccc tca cta aag gga ata agc ttg cgg ccg ctg tcc tcg ctg tgg tcg   48
Pro Ser Leu Lys Gly Ile Ser Leu Arg Pro Leu Ser Ser Leu Trp Ser
 1               5                  10                  15

cct ctg ttg ctc tgt gtc ctc ggg gtg cct cgg ggc gga tcg gga gcc   96
Pro Leu Leu Leu Cys Val Leu Gly Val Pro Arg Gly Gly Ser Gly Ala
            20                  25                  30

cac aca gct gta atc agc ccc cag gac ccc acc ctt ctc atc ggc tcc  144
His Thr Ala Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser
        35                  40                  45

tcc ctg caa gct acc tgc tct ata cat gga gac aca cct ggg gcc acc  192
Ser Leu Gln Ala Thr Cys Ser Ile His Gly Asp Thr Pro Gly Ala Thr
    50                  55                  60

gct gag ggg ctc tac tgg acc ctc aat ggt cgc cgc ctg ccc tct gag  240
Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly Arg Arg Leu Pro Ser Glu
65                  70                  75                  80

ctg tcc cgc ctc ctt aac acc tcc acc ctg gcc ctg gcc ctg gct aac  288
Leu Ser Arg Leu Leu Asn Thr Ser Thr Leu Ala Leu Ala Leu Ala Asn
                85                  90                  95

ctt aat ggg tcc agg cag cag tca gga gac aat ctg gtg tgt cac gcc  336
Leu Asn Gly Ser Arg Gln Gln Ser Gly Asp Asn Leu Val Cys His Ala
            100                 105                 110

cga gat ggc agc att ctg gct ggc tcc tgc ctc tat gtt ggc ttg ccc  384
Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro
        115                 120                 125

cct gag aag cct ttt aac atc agc tgc tgg tcc cgg aac atg aag gat  432
Pro Glu Lys Pro Phe Asn Ile Ser Cys Trp Ser Arg Asn Met Lys Asp
    130                 135                 140

ctc acg tgc cgc tgg aca ccg ggt gca cac ggg gag aca ttc tta cat  480
Leu Thr Cys Arg Trp Thr Pro Gly Ala His Gly Glu Thr Phe Leu His
145                 150                 155                 160

acc aac tac tcc ctc aag tac aag ctg agg tgg tac ggt cag gat aac  528
Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn
                165                 170                 175

aca tgt gag gag tac cac act gtg ggc cct cac tca tgc cat atc ccc  576
Thr Cys Glu Glu Tyr His Thr Val Gly Pro His Ser Cys His Ile Pro
            180                 185                 190

aag gac ctg gcc ctc ttc act ccc tat gag atc tgg gtg gaa gcc acc  624
Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr
        195                 200                 205

aat cgc cta ggc tca gca aga tct gat gtc ctc aca ctg gat gtc ctg  672
Asn Arg Leu Gly Ser Ala Arg Ser Asp Val Leu Thr Leu Asp Val Leu
    210                 215                 220

gac gtg gtg acc acg gac ccc cca ccc gac gtg cac gtg agc cgc gtt  720
Asp Val Val Thr Thr Asp Pro Pro Pro Asp Val His Val Ser Arg Val
225                 230                 235                 240
```

```
ggg ggc ctg gag gac cag ctg agt gtg cgc tgg gtc tca cca cca gct   768
Gly Gly Leu Glu Asp Gln Leu Ser Val Arg Trp Val Ser Pro Pro Ala
                245                 250                 255

ctc aag gat ttc ctc ttc caa gcc aag tac cag atc cgc tac cgc gtg   816
Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val
            260                 265                 270

gag gac agc gtg gac tgg aag gtg gtg gat gac gtc agc aac cag acc   864
Glu Asp Ser Val Asp Trp Lys Val Val Asp Asp Val Ser Asn Gln Thr
        275                 280                 285

tcc tgc cgt ctc gcg ggc ctg aag ccc ggc acc gtt tac ttc gtc caa   912
Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly Thr Val Tyr Phe Val Gln
    290                 295                 300

gtg cgt tgt aac cca ttc ggg atc tat ggg tcg aaa aag gcg gga atc   960
Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile
305                 310                 315                 320

tgg agc gag tgg agc cac ccc acc gct gcc tcc acc cct cga agt gag  1008
Trp Ser Glu Trp Ser His Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu
                325                 330                 335

cgc ccg ggc ccg ggc ggc ggg gtg tgc gag ccg cgg ggc ggc gag ccc  1056
Arg Pro Gly Pro Gly Gly Gly Val Cys Glu Pro Arg Gly Gly Glu Pro
            340                 345                 350

agc tcg ggc ccg gtg cgg cgc gag ctc aag cag ttc ctc ggc tgg ctc  1104
Ser Ser Gly Pro Val Arg Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu
        355                 360                 365

aag aag cac gca tac tgc tcg aac ctt agt ttc cgc ctg tac gac cag  1152
Lys Lys His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln
    370                 375                 380

tgg cgt gct tgg atg cag aag tca cac aag acc cga aac cag gac gag  1200
Trp Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln Asp Glu
385                 390                 395                 400

ggg atc ctg ccc tcg ggc aga cgg ggt gcg gcg aga ggt cct gcc ggc  1248
Gly Ile Leu Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly
                405                 410                 415

taaactctaa ggataggcca tcctcctgct gggtcagacc tggaggctca cctgaattgg 1308

agcccctctg taccatctgg gcaacaaaga aacctaccag aggctggggc acaatgagct 1368

cccacaacca cagctttggt ccacatgatg gtcacacttg gatatacccc agtgtgggta 1428

gggttggggt attgcagggc ctcccaagag ttttttaaa taaataaagg agttgttcag 1488

gtcccgatgg naaaaaaaaa aaaaaaaaaa aaaaaa                           1524
```

Table 5: Alignment of primate, e.g., human, and rodent, e.g., mouse, DSRS1 (SEQ ID NO: 9 and 11):

```
hDSRS1   MPAGRRGPAA QSARRPPPLL PLLLLLCVLG APRAGSGAHT AVISPQDPTL
mDSRS1   .......... ....RPLSSL WSPLLLCVLG VPRGGSGAHT AVISPQDPTL

hDSRS1   LIGSSLLATC SVHGDPPGAT AEGLYWTLNG RRLPPELSRV LNASTLALAL
mDSRS1   LIGSSLQATC SIHGDTPGAT AEGLYWTLNG RRLPSELSRL LNTSTLALAL

hDSRS1   ANLNGSRQRS GDNLVCHARD GSILAGSCLY VGLPPEKPVN ISCWSKNMKD
mDSRS1   ANLNGSRQQS GDNLVCHARD GSILAGSCLY VGLPPEKPFN ISCWSRNMKD

hDSRS1   LTCRWTPGAH GETFLHTNYS LKYKLRWYGQ DNTCEEYHTV GPHSCHIPKD
mDSRS1   LTCRWTPGAH GETFLHTNYS LKYKLRWYGQ DNTCEEYHTV GPHSCHIPKD

hDSRS1   LALFTPYEIW VEATNRLGSA RSDVLTLDIL DVVTTDPPPD VHVSRVGGLE
mDSRS1   LALFTPYEIW VEATNRLGSA RSDVLTLDVL DVVTTDPPPD VHVSRVGGLE

hDSRS1   DQLSVRWVSP PALKDFLFQA KYQIRYRVED SVDWKVVDDV SNQTSCRLAG
mDSRS1   DQLSVRWVSP PALKDFLFQA KYQIRYRVED SVDWKVVDDV SNQTSCRLAG

hDSRS1   LKPGTVYFVQ VRCNPFGIYG SKKAGIWSEW SHPTAASTPR SERPGPGGGA
mDSRS1   LKPGTVYFVQ VRCNPFGIYG SKKAGIWSEW SHPTAASTPR SERPGPGGGV

hDSRS1   CEPRGGEPSS GPVRRELKQF LGWLKKHAYC SNLSFRLYDQ WRAWMQKSHK
mDSRS1   CEPRGGEPSS GPVRRELKQF LGWLKKHAYC SNLSFRLYDQ WRAWMQKSHK

hDSRS1   TRNQ...VLP DKL..... ..
mDSRS1   TRNQDEGILP SGRRGAARGP AG
```

Table 6: Primate, e.g., human, IL-B30 nucleotide and polypeptide sequences. Predicted signal cleavage site indicated, but may actually be a residue or more to either side, depending upon the cell (SEQ ID NO: 16 and 17):

```
atg ctg ggg agc aga gct gta atg ctg ctg ttg ctg ctg ccc tgg aca   48
Met Leu Gly Ser Arg Ala Val Met Leu Leu Leu Leu Pro Trp Thr
    -20                 -15                 -10

gct cag ggc aga gct gtg cct ggg ggc agc agc cct gcc tgg act cag   96
Ala Gln Gly Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln
 -5              -1   1               5                  10

tgc cag cag ctt tca cag aag ctc tgc aca ctg gcc tgg agt gca cat   144
Cys Gln Gln Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His
             15                  20                  25

cca cta gtg gga cac atg gat cta aga gaa gag gga gat gaa gag act   192
Pro Leu Val Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr
         30                  35                  40
```

```
aca aat gat gtt ccc cat atc cag tgt gga gat ggc tgt gac ccc caa   240
Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln
     45                  50                  55

gga ctc agg gac aac agt cag ttc tgc ttg caa agg atc cac cag ggt   288
Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly
 60                  65                  70                  75

ctg att ttt tat gag aag ctg cta gga tcg gat att ttc aca ggg gag   336
Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu
                 80                  85                  90

cct tct ctg ctc cct gat agc cct gtg gcg cag ctt cat gcc tcc cta   384
Pro Ser Leu Leu Pro Asp Ser Pro Val Ala Gln Leu His Ala Ser Leu
             95                 100                 105

ctg ggc ctc agc caa ctc ctg cag cct gag ggt cac cac tgg gag act   432
Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
        110                 115                 120

cag cag att cca agc ctc agt ccc agc cag cca tgg cag cgt ctc ctt   480
Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu
    125                 130                 135

ctc cgc ttc aaa atc ctt cgc agc ctc cag gcc ttt gtg gct gta gcc   528
Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala
140                 145                 150                 155

gcc cgg gtc ttt gcc cat gga gca gca acc ctg agt ccc taa           570
Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro
                160                 165
```

```
MLGSRAVMLL LLLPWTAQGR AVPGGSSPAW TQCQQLSQKL CTLAWSAHPL VGHMDLREEG
DEETTNDVPH IQCGDGCDPQ GLRDNSQFCL QRIHQGLIFY EKLLGSDIFT GEPSLLPDSP
VAQLHASLLG LSQLLQPEGH HWETQQIPSL SPSQPWQRLL LRFKILRSLQ AFVAVAARVF
AHGAATLSP
```

Rodent, e.g., mouse, nucleotide and polypeptide sequences of IL-B30. Predicted signal cleavage site indicated, but may actually be a residue or more to either side, depending upon the cell (SEQ ID NO: 18 and 19):

```
cgcttagaag tcggactaca gagttagact cagaaccaaa ggaggtggat agggggtcca 60

caggcctggt gcagatcaca gagccagcca gatctgagaa gcagggaaca ag atg ctg 118
                                                        Met Leu
                                                         -20

gat tgc aga gca gta ata atg cta tgg ctg ttg ccc tgg gtc act cag   166
Asp Cys Arg Ala Val Ile Met Leu Trp Leu Leu Pro Trp Val Thr Gln
                -15                 -10                 -5

ggc ctg gct gtg cct agg agt agc agt cct gac tgg gct cag tgc cag   214
Gly Leu Ala Val Pro Arg Ser Ser Ser Pro Asp Trp Ala Gln Cys Gln
         -1   1                  5                  10

cag ctc tct cgg aat ctc tgc atg cta gcc tgg aac gca cat gca cca   262
Gln Leu Ser Arg Asn Leu Cys Met Leu Ala Trp Asn Ala His Ala Pro
     15                  20                  25
```

```
gcg gga cat atg aat cta cta aga gaa gaa gag gat gaa gag act aaa   310
Ala Gly His Met Asn Leu Leu Arg Glu Glu Glu Asp Glu Glu Thr Lys
 30                  35                  40                  45

aat aat gtg ccc cgt atc cag tgt gaa gat ggt tgt gac cca caa gga   358
Asn Asn Val Pro Arg Ile Gln Cys Glu Asp Gly Cys Asp Pro Gln Gly
                 50                  55                  60

ctc aag gac aac agc cag ttc tgc ttg caa agg atc cgc caa ggt ctg   406
Leu Lys Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile Arg Gln Gly Leu
               65                  70                  75

gct ttt tat aag cac ctg ctt gac tct gac atc ttc aaa ggg gag cct   454
Ala Phe Tyr Lys His Leu Leu Asp Ser Asp Ile Phe Lys Gly Glu Pro
          80                  85                  90

gct cta ctc cct gat agc ccc atg gag caa ctt cac acc tcc cta cta   502
Ala Leu Leu Pro Asp Ser Pro Met Glu Gln Leu His Thr Ser Leu Leu
     95                 100                 105

gga ctc agc caa ctc ctc cag cca gag gat cac ccc cgg gag acc caa   550
Gly Leu Ser Gln Leu Leu Gln Pro Glu Asp His Pro Arg Glu Thr Gln
110                 115                 120                 125

cag atg ccc agc ctg agt tct agt cag cag tgg cag cgc ccc ctt ctc   598
Gln Met Pro Ser Leu Ser Ser Ser Gln Gln Trp Gln Arg Pro Leu Leu
                130                 135                 140

cgt tcc aag atc ctt cga agc ctc cag gcc ttt ttg gcc ata gct gcc   646
Arg Ser Lys Ile Leu Arg Ser Leu Gln Ala Phe Leu Ala Ile Ala Ala
            145                 150                 155

cgg gtc ttt gcc cac gga gca gca act ctg act gag ccc tta gtg cca   694
Arg Val Phe Ala His Gly Ala Ala Thr Leu Thr Glu Pro Leu Val Pro
        160                 165                 170

aca gct taaggatgcc caggttccca tggctaccat gataagacta atctatcagc    750
Thr Ala
    175

ccagacatct accagttaat taacccatta ggacttgtgc tgttcttgtt tcgtttgttt 810

tgcgtgaagg gcaaggacac cattattaaa gagaaaagaa acaaacccca gagcaggcag 870

ctggctagag aaaggagctg gagaagaaga ataaagtctc gagcccttgg ccttggaagc 930

gggcaagcag ctgcgtggcc tgaggggaag ggggcggtgg catcgagaaa ctgtgagaaa 990

acccagagca tcagaaaaag tgagcccagg ctttggccat tatctgtaag aaaaacaaga 1050

aaaggggaac attatacttt cctgggtggc tcagggaaat gtgcagatgc acagtactcc 1110

agacagcagc tctgtacctg cctgctctgt ccctcagttc taacagaatc tagtcactaa 1170

gaactaacag gactaccaat acgaactgac aaa                              1203

MLDCRAVIML WLLPWVTQGL AVPRSSSPDW AQCQQLSRNL CMLAWNAHAP AGHMNLLREE
EDEETKNNVP RIQCEDGCDP QGLKDNSQFC LQRIRQGLAF YKHLLDSDIF KGEPALLPDS
PMEQLHTSLL GLSQLLQPED HPRETQQMPS LSSSQQWQRP LLRSKILRSL QAFLAIAARV
FAHGAATLTE PLVPTA
```

Partial polypeptide sequence of IL-B30 from pig (SEQ ID NO: 20):

```
Ser Cys Leu Gln Arg Ile His Gln Gly Leu Val Phe Tyr Glu Lys Leu
 1               5                  10                  15

Leu Gly Ser Asp Ile Phe Thr Gly Glu Pro Ser Leu His Pro Asp Gly
            20                  25                  30

Ser Val Gly Gln Leu His Ala Ser Leu Leu Gly Leu Arg Gln Leu Leu
        35                  40                  45

Gln Pro Glu Gly His His Trp Glu Thr Glu Gln Thr Pro Ser Pro Ser
    50                  55                  60

Pro Ser Gln Pro Trp Gln Arg Leu Leu Leu Arg Leu Lys Ile Leu Arg
65                  70                  75                  80

Ser Leu Gln Ala Phe Val Ala Val Ala Ala Arg Val Phe Ala His Gly
                85                  90                  95

Ala Ala Thr Leu Ser Gln
            100
```

SCLQRIHQGLVFYEKLLGSDIFTGEPSLHPDGSVGQLHASLLGLRQLLQPEGHHWETEQTPSPSPSQ
PWQRLLLRLKILRSLQAFVAVAARVFAHGAATLSQ

Table 2 shows comparison of the available sequences of primate and rodent embodiments of DCRS1. Table 3 shows the alignment of the DCRS1 with other cytokine receptor subunits. The DCRS1 shows particular similarity to the IL-12 receptor subunit beta, though it may be aligned with the gp130 (IL-6 receptor beta) and G-CSF receptor (alpha) subunits. The similarity to the IL-12 receptor subunit suggests that the functional receptor incorporating the DCRS1 may be similar to the IL-12 receptor. The IL-12 receptor alpha subunit is a soluble subunit. The DSRS1 is likely to be the corresponding soluble subunit, which would initially interact with ligand, e.g., the IL-B30, and then form a functional complex with the DCRS1. See, e.g., Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007. Alternatively, the soluble subunit may interact with the transmembrane receptor subunit, which then could bind ligand.

Table 4 provides the nucleotide and polypeptide sequences of two species embodiments of a soluble receptor subunit designated DNAX Soluble Receptor Subunit 1 (DSRS1).

These align with and exhibit features in common with other cytokine receptor alpha type subunits. These subunits are believed to interact with the corresponding DCRS1 to form a functional receptor when the receptor ligand is present. Note that relatively close sequence similarity of the DCRS1 is with gp130, which is the beta subunit of the IL-6 receptor. Applicants believe that the ligand for the receptor is likely the ligand designated IL-B30, whose sequence is near to G-CSF and IL-6. See USSN 60/053,765, which is incorporated herein by reference.

Table 5 shows alignment of the DSRS1 from the primate and rodent species. Applicants believe that this soluble subunit forms a dimer, and binds to its dimerized ligand, which then combines with a beta type homo or heterodimer. Alternatively, the soluble subunit may bind to the transmembrane subunit(s), and then bind ligand.

Structural features of the human DCRS1, and similarly for the other receptors as aligned in Table 3, include characteristic Ig domains from about (SEQ ID NO: 2) val1 to pro133; fibronectin domains corresponding to the DCRS1 sequence from about gly134 to pro232, gly233 to gly306, and pro307 to lys403; a transmembrane segment from about val404 to gly427; and an intracellular domain from about arg428 to the carboxy terminus. Of particular interest is the WGEWS motif corresponding to residues trp104 to ser108. In many contexts, various variants and fragments will be equivalent to the described DSRS1.

As used herein, the term DCRS1 shall be used to describe a protein comprising the amino acid sequence shown in Table 1. In many cases, a substantial fragment thereof will be functionally or structurally equivalent, including, e.g., an extracellular or intracellular domain. The invention also includes a protein variation of the respective DCRS1 allele whose sequence is provided, e.g., a mutein or soluble extracellular construct. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold

substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein. Preferred forms of the receptor complexes will bind the appropriate ligand with an affinity and selectivity appropriate for a ligand-receptor interaction.

This invention also encompasses combinations of proteins or peptides having substantial amino acid sequence identity with the amino acid sequence in Table 1. It will include sequence variants with relatively few substitutions, e.g., preferably less than about 3-5. Other embodiments include forms in association with an alpha subunit, e.g., a DSRS1, and/or with ligand, e.g., IL-B30.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of different proteins can be compared to one another over appropriate length stretches. In many situations, fragments may exhibit functional properties of the intact subunits, e.g., the extracellular domain of the

transmembrane receptor may retain the ligand binding features, and may be used to prepare a soluble receptor-like complex.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduces, as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative substitutions are included) with an amino acid sequence segment of Table 1. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in Table 1.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by cytokine-like ligands. For example, these receptors should mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates. The subunits may also be functional immunogens to elicit recognizing antibodies, or antigens capable of binding antibodies.

The terms ligand, agonist, antagonist, and analog of, e.g., a DCRS1, include molecules that modulate the characteristic cellular responses to cytokine ligand proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are typically mediated through receptor tyrosine kinase pathways.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. See, e.g., Herz, et al. (1997) J. Recept. Signal Transduct. Res. 17:671-776; and Chaiken, et al. (1996) Trends Biotechnol. 14:369-375. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

II. Activities

The cytokine receptor-like proteins will have a number of different biological activities, e.g., modulating cell proliferation, or in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect. The subunit will probably have a specific low affinity binding to the ligand.

The DCRS1 has the characteristic motifs of a receptor signaling through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171.

The biological activities of the cytokine receptor subunits will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The receptor subunits may combine to form functional complexes, e.g., which may be useful for binding ligand or preparing antibodies. These will have substantial diagnostic uses, including detection or quantitation.

III. Nucleic Acids

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNAs which encode combinations of such proteins or polypeptides having characteristic sequences, e.g., of the DCRS1s. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in Table 1, but preferably not with a corresponding segment of other receptors described in Table 3. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., exhibiting significant stretches of identity, to one shown in Table 1. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are

equivalent to the DCRS1 proteins. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene. Combinations, as described, are also provided.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as

found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DCRS1 and fusions of sequences from various different related molecules, e.g., other cytokine receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily at least 30 nucleotides, more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic sequences can be compared to one

another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for the DCRS1 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be more useful.

Nucleic acids encoding various combinations including, e.g., the DSRS1, the DCRS1, and/or the IL-B30, will be useful for coexpression of the proteins together. Such will be useful, e.g., in producing complexes, for production of antibodies or screening for ligands.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., DCRS1 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical

when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from Table 1. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 246, 273, and other lengths.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of

about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DCRS1-like derivatives include predetermined or site-specific mutations of the protein or its fragments, including silent mutations using genetic code degeneracy. "Mutant DCRS1" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DCRS1 as set forth above, but having an amino acid sequence which differs from that of other cytokine receptor-like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DCRS1" encompasses a protein having substantial sequence identity with a protein of Table 1, and typically shares most of the biological activities or effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DCRS1 mutagenesis can be achieved by making

amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy-terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DCRS1 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

Certain embodiments of the invention are directed to combination compositions comprising the receptor or ligand sequences described. In other embodiments, functional portions of the sequences may be joined to

encode fusion proteins. In other forms, variants of the described sequences may be substituted in the combinations.

IV. Proteins, Peptides

As described above, the present invention encompasses primate DCRS1, e.g., whose sequences are disclosed in Table 1, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including, e.g., epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these primate or rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of a DCRS1 with another cytokine receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences. Combinations of various designated proteins into complexes are also provided.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., cytokine receptors or Toll-like receptors, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand

binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference. In particular, combinations of polypeptide sequences provided in Tables 1, 4, or 6 are particularly preferred. Variant forms of the proteins may be substituted in the described combinations. In certain embodiments, portions of the DSRS1 may be fused to portions of the IL-B30.

The present invention particularly provides muteins which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DCRS1 with other members of the cytokine receptor family show conserved features/residues. See Table 3. Alignment of the human DCRS1 sequence with other members of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling activities; and conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of the primate DCRS1 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the DCRS1 amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties, including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different cytokine ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial ß-galactosidase, trpE, Protein A, ß-lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. Labeled proteins will often be substituted in the described combinations of proteins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DCRS1 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth

chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A combination, e.g., including a DCRS1, of this invention can be used as an immunogen for the production of antisera or antibodies specific, e.g., capable of distinguishing between other cytokine receptor family members, for the combinations described. The complexes can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified DCRS1 can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DCRS1 fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in Table 1, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of the native DCRS1. Complexes of combinations of proteins will also be useful, and antibody preparations thereto can be made.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the

effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor complexes or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., in Table 1. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a

pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins. Combinations of the described proteins, or nucleic acids encoding them, are particularly interesting.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The multiple genes may be coordinately expressed, and may be on a polycistronic message. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a combination of proteins, as described, or a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNAs coding for such proteins in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNAs are inserted into the vector such that growth of the host containing the vector expresses the cDNAs in question. Usually, expression

vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding portions into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired proteins, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject proteins. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the proteins to accumulate. The proteins can be recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their

Uses, (eds. Rodriguez and Denhardt), Buttersworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DCRS1 sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin or receptor proteins. In principle, many higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually

include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins and some membrane proteins, an open reading frame usually encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690 and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser et al. (1987) Science 235:312-317. The mature proteins of the invention can be readily determined using standard methods.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes.

Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells. Expression in prokaryote cells will typically lead to unglycosylated forms of protein.

The source of DCRS1 can be a eukaryotic or prokaryotic host expressing recombinant DCRS1, such as is described above. The source can also be a cell line such as mouse Swiss 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate DCRS1, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial DCRS1 sequences.

The DCRS1 proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being

used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells

producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate. Individual proteins may be purified and thereafter combined.

VI. Antibodies

Antibodies can be raised to the various mammalian, e.g., primate DCRS1 proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 µM, typically at least about 100µM, more typically at least about 30 µM, preferably at least about 10 µM, and more preferably at least about 3 µM or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein. Likewise, nucleic acids and proteins may be immobilized to solid substrates for affinity purification or detection methods. The substrates may be, e.g., solid resin beads or sheets of plastic.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian cytokine receptors and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera.

A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is hereby incorporated herein by

reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references are incorporated herein by reference.

The antibodies of this invention can also be used for affinity chromatography in isolating the DCRS1 proteins or peptides. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. Alternatively, the protein may be used to purify antibody. Appropriate cross absorptions or depletions may be applied.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against a cytokine receptor will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various

immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A cytokine receptor protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 13, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 13. This antiserum is selected to have low crossreactivity against other cytokine receptor family members, e.g., IL-12 receptor beta or gp130, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 13, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other cytokine receptor family members, e.g., IL-12 receptor beta and/or gp130, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two cytokine receptor family members are used in

this determination. These cytokine receptor family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 13 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the proteins of IL-12 receptor beta or gp130. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the DCRS1 like protein of SEQ ID NO: 13). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of the selected protein or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these cytokine receptor proteins are members of a family of homologous proteins that comprise at least 6 so far identified genes. For a particular gene product, such as the DCRS1, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-

allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring DCRS1 protein. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect, e.g., upon transfected lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the cytokine receptor family as a whole. By aligning a protein optimally with the protein of the cytokine receptors and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

While many of the descriptions above (and below) are directed to individual proteins, they may be applied to complexes, e.g., natural or functional, of proteins.

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the cytokine receptor like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773,

which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble cytokine receptors in an active state such as is provided by this invention.

Purified DCRS1 can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of DCRS1, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a DCRS1 peptide or gene segment or a reagent which recognizes one or the other. Typically, recognition reagents, in the case of peptide, would be a receptor or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of DCRS1 in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding affinity for DCRS1, a source of DCRS1 (naturally occurring or recombinant) as a positive control, and a means for separating the bound from free labeled compound, for example a solid phase for immobilizing the DCRS1 in the test sample. Compartments containing reagents, and instructions, will normally be provided. Appropriate nucleic acid or protein containing kits are also provided.

Antibodies, including antigen binding fragments, specific for mammalian DCRS1 or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a cytokine receptor or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991 and periodic supplements) Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of cytokine receptors. These should be useful as therapeutic reagents under appropriate circumstances.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where

the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, cytokine receptor, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I, enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The cytokine receptor can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as

described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of an cytokine receptor. These sequences can be used as probes for detecting levels of the respective cytokine receptor in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P. However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of

antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

This invention provides reagents with significant therapeutic value. See, e.g., Levitzki (1996) Curr. Opin. Cell Biol. 8:239-244. The cytokine receptors (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. For example, the IL-1 ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; and Hultmark (1994) Nature 367:116-117.

Recombinant cytokine receptors, muteins, agonist or antagonist antibodies thereto, or antibodies can be

purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using cytokine receptor or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to cytokine receptors as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon

Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μM concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

Cytokine receptors, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those

suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other cytokine receptor family members.

IX. Screening

Drug screening using DCRS1 or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunit, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of a cytokine ligand. This invention further contemplates the therapeutic use of antibodies to the receptor as cytokine agonists or antagonists.

Similarly, complexes comprising multiple proteins may be used to screen for ligands or reagents capable of recognizing the complex. Most cytokine receptors comprise at least two subunits, which may be the same, or distinct. Alternatively, the transmembrane receptor may

bind to a complex comprising a cytokine-like ligand associated with another soluble protein serving, e.g., as a second receptor subunit. In such a case, the DCRS1 may bind to a complex of the IL-B30 with the DSRS1.

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing the DCRS1 in combination with the DSRS1. Cells may be isolated which express a receptor in isolation from other functional receptors. Such cells, either in viable or fixed form, can be used for standard antibody/antigen or ligand/receptor binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of putative ligand) are contacted and incubated with a labeled receptor or antibody having known binding affinity to the ligand, such as ^{125}I-antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of ligand binding. The amount of test compound bound is inversely proportional to the amount of labeled receptor binding to the known source. Many techniques can be used to separate bound from free ligand to assess the degree of ligand binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on cytokine mediated functions, e.g., second messenger levels, i.e., Ca^{++}; cell proliferation; inositol phosphate pool changes; and others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system. Calcium sensitive dyes will be useful for

detecting Ca^{++} levels, with a fluorimeter or a fluorescence cell sorting apparatus.

X. Ligands

The descriptions of the DCRS1 herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling cytokine receptor, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available cytokine receptor sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Generally, descriptions of cytokine receptors will be analogously applicable to individual specific embodiments directed to DCRS1 reagents and compositions. Alternatively, the DCRS1 might bind to a soluble complex of the DSRS1 with another ligand. Thus, expression cloning of a cotransfectant of a library with the DSRS1 may express combinations of the DSRS1 with cytokine-like ligand, to form the soluble complex, which binds to the DCRS1.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

EXAMPLES

I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-10 or IL-12 receptors may be applied to the DCRS1, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference.

II. Computational Analysis

Human sequences related to cytokine receptors were identified from genomic sequence database using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). Standard analysis programs may be used to evaluate structure, e.g., PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310). Standard comparison software includes, e.g., Altschul, et al. (1990) J. Mol. Biol. 215:403-10; Waterman (1995) Introduction to Computational Biology: Maps, Sequences, and Genomes Chapman & Hall; Lander and Waterman (eds. 1995) Calculating the Secrets of Life: Applications of the Mathematical Sciences in Molecular Biology National Academy Press; and Speed and Waterman (eds. 1996) Genetic Mapping and DNA Sequencing (Ima Volumes in Mathematics and Its Applications, Vol 81) Springer Verlag.

III. Cloning of full-length DCRS1 cDNAs; Chromosomal localization

PCR primers derived from the DCRS1 sequence are used to probe a human cDNA library. Sequences may be derived, e.g., from Table 1, preferably those adjacent the ends of incomplete sequences. Full length cDNAs for primate, rodent, or other species DCRS1 are cloned, e.g., by DNA hybridization screening of λgt10 phage. PCR reactions are conducted using T. aquaticus Taqplus DNA polymerase (Stratagene) under appropriate conditions.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine was added for the final seven hours of culture (60 μg/ml of

medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^{3}H. The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB_2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Similar appropriate methods are used for other species.

IV. Localization of DCRS1 mRNA

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2 μg of poly(A)$^+$ RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [α-^{32}P] dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations are performed at 65° C in 0.5 M Na_2HPO_4, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southerns are performed with selected human DCRS1 clones to examine their expression in hemopoietic or other cell subsets.

Alternatively, two appropriate primers are selected from Table 1. RT-PCR is used on an appropriate mRNA

sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected by PCR signal. Northern blots can be performed.

Message for genes encoding DCRS1 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the cytokine ligands.

For mouse distribution, e.g., Southern Analysis can be performed: DNA (5 µg) from a primary amplified cDNA library was digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for mouse mRNA isolation may include: resting mouse fibroblastic L cell line (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 µg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last

stimulation with antigen (T207); TH2 T cell clone CDC35, 10 μg/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled(M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongulus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).

Samples for human mRNA isolation may include: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN-γ, TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random γδ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 4, 16

h pooled (M106); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNFα, monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

Similar samples may isolated in other species for evaluation.

V. Cloning of species counterparts of DCRS1

Various strategies are used to obtain species counterparts of the DCRS1, preferably from other primates or rodents. One method is by cross hybridization using closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between genes, e.g., areas of highly conserved or nonconserved polypeptide or nucleotide sequence.

VI. Production of mammalian DCRS1 protein

An appropriate, e.g., GST, fusion construct is engineered for expression, e.g., in E. coli. For example, a mouse IGIF pGex plasmid is constructed and transformed into E. coli. Freshly transformed cells are grown, e.g., in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction, the bacteria are harvested and the pellets containing the DCRS1 protein are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the cytokine receptor protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. The fractions containing the DCRS1-GST fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DCRS1 are pooled and diluted in cold distilled H_2O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column. Fractions containing the

DCRS1 protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with cytokine receptor protein may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

VII. Determining physiological forms of receptors

The cellular forms of receptors for ligands can be tested with the various ligands and receptor subunits provided. In particular, multiple cytokine receptor like ligands have been identified. The IL-B30 cytokine has been described. See above.

Cotransformation of the DCRS1 with putative other receptor subunits may be performed. In particular, the DSRS1 is suggested to be a second receptor subunit needed for functional receptor signaling. Such cells may be used to screen putative cytokine ligands, such as the IL-B30, for signaling. A cell proliferation assay may be used. In fact, the DSRS1 may combine with the IL-B30 to form a soluble cytokine-receptor subunit complex, which then binds to the DCRS1.

In addition, it has been known that many cytokine receptors function as heterodimers. The IL-1α and IL-1β ligands bind an IL-1R1 as the primary receptor and this complex then forms a high affinity receptor complex with the IL-1R3. As indicated above, the sequence similarity to IL-12 receptor subunits suggests functional similarity of the functional receptor, e.g., a soluble alpha subunit, and transmembrane beta subunit.

These subunit combinations can be tested now with the provided reagents. In particular, appropriate constructs can be made for transformation or transfection of subunits into cells. Constructs for the alpha chains, e.g., DSRS1 forms, can be made. Likewise for the beta subunit DCRS1. Combinatorial transfections of transformations can make cells expressing defined subunits, which can be tested for response to the predicted ligands. Appropriate cell types can be used,

e.g., 293 T cells, with, e.g., an NFkb reporter construct.

Biological assays will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme reactions, and may mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The family of cytokines contains molecules which are important mediators of hematopoiesis or inflammatory disease. See, e.g., Thomson (ed. 1994) The Cytokine Handbook Academic Press, San Diego; and Dinarello (1996) Blood 87:2095-2147.

VIII. Preparation of antibodies specific for DCRS1

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DCRS1 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response. Serum or antibody preparations may be cross-absorbed or

immunoselected to prepare substantially purified antibodies of defined specificity and high affinity.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the DCRS1, e.g., by ELISA or other assay. Antibodies which specifically recognize specific DCRS1 embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (ed. 1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang, et al. (1995) Immunity 2: 129-135.

Moreover, antibodies which may be useful to determine the combination of the DCRS1 with a functional alpha subunit may be generated. Thus, e.g., epitopes characteristic of a particular functional alpha/beta combination may be identified with appropriate antibodies.

IX. Production of fusion proteins with DCRS1

Various fusion constructs are made with DCRS1. A portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective cytokine receptor. The two hybrid system may also be used to isolate proteins which specifically bind to DCRS1.

X. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

XI. Isolation of a ligand for DCRS1

A cytokine receptor can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. The binding receptor may be a heterodimer of receptor subunits; or may involve, e.g., a complex of the DCRS1 with DSRS1. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at 2-3 x 10^5 cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DCRS1-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN_3 for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DCRS1 or DCRS1/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and

preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand, e.g., either IL-B30 alone or a complex of IL-B30 with DSRS1, can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DCRS1 fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by mammalian DCRS1. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A composition comprising:

a) both:

i) a DSRS1 protein; and

ii) an isolated or recombinant DCRS1 protein;

b) both:

i) an isolated or recombinant DSRS1 protein; and

ii) a DCRS1 protein; or

c) both:

i) a substantially pure or recombinant IL-B30 protein; and

ii) a DCRS1 protein.

2. The composition of Claim 1, wherein:

a) said DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11;

b) said DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or

c) said IL-B30 has sequence of mature SEQ ID NO: 17 or 19; or

d) at least one of said proteins:

i) is unglycosylated;

ii) is made with synthetic methods;

iii) has a detectable label;

iv) is attached to a solid substrate; or

v) is conjugated to another chemical moiety.

3. A composition comprising:

a) a substantially pure DCRS1 protein and:

i) a DSRS1 protein; or

ii) an IL-B30 cytokine protein; or

b) a DCRS1 protein and a substantially pure:

i) DSRS1 protein; or

ii) IL-B30 cytokine protein.

4. The composition of Claim 3 comprising said DCRS1 and said DSRS1 proteins, wherein said proteins combine to bind IL-B30 with high affinity.

5. A sterile composition of Claim 3.

6. A kit comprising said proteins of Claim 3, and:
a) a compartment comprising two or more of said proteins;
b) a compartment comprising a soluble receptor alpha subunit;
c) a compartment comprising an IL-B30 cytokine protein; or
d) instructions for use or disposal of reagents in said kit.

7. A binding composition comprising the antigen binding sites from antibodies, which antibodies bind to an epitope found on a composition of Claim 1, but not on separate proteins thereof.

8. The binding composition of Claim 7, wherein:
a) said DCRS1 is:
i) a primate protein;
ii) a purified human or mouse DCRS1; or
iii) a mature polypeptide of Table 1;
b) said DSRS1 is:
i) a primate protein;
ii) a purified human or mouse DSRS1; or
iii) a mature polypeptide of Table 4; or
c) said IL-B30 is:
i) a primate protein;
ii) a purified human or mouse IL-B30; or
iii) a mature polypeptide of Table 6.

9. The binding composition of Claim 7, wherein said binding composition:

a) is in a container;

b) is an Fv, Fab, or Fab2 fragment;

c) is conjugated to another chemical moiety;

d) is immunoselected;

e) is a polyclonal antibody;

f) exhibits a Kd to antigen of at least 30 μM;

g) is attached to a solid substrate, including a bead or plastic membrane;

h) is in a sterile composition; or

i) is detectably labeled, including a radioactive or fluorescent label.

10. A kit comprising said binding composition of Claim 7, and:

a) a compartment comprising said binding composition;

b) a compartment comprising said DCRS1, DSRS1, or IL-B30 protein; or

c) instructions for use or disposal of reagents in said kit.

11. An isolated or recombinant nucleic acid encoding:

a) both:

i) a DSRS1 protein; and

ii) a DCRS1 protein;

b) both:

i) a DSRS1 protein; and

ii) an IL-B30 protein; or

c) both:

i) a DCRS1 protein; and

ii) an IL-B30 protein.

12. The nucleic acid of Claim 11, which encodes both a DCRS1 protein and a DSRS1 protein.

13. The nucleic acid of Claim 11, which encodes both a DSRS1 protein and an IL-B30.

14. The nucleic acid of Claim 11, which is an expression vector.

15. The nucleic acid of Claim 11, wherein:

a) said DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11;

b) said DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or

c) said IL-B30 has sequence of mature SEQ ID NO: 17 or 19.

16. The nucleic acid of Claim 11, comprising the coding portion of:

a) SEQ ID NO: 8 or 10;

b) SEQ ID NO: 12 or 14; or

c) SEQ ID NO: 16 or 18.

17. A cell comprising said recombinant nucleic acid of Claim 11.

18. The cell of Claim 17, wherein said cell is:

a) a prokaryotic cell;

b) a eukaryotic cell;

c) a bacterial cell;

d) a yeast cell;

e) an insect cell;

f) a mammalian cell;

g) a mouse cell;

h) a primate cell; or

i) a human cell.

19. A method of producing a receptor complex, comprising culturing a cell of Claim 17 in an environment resulting in expression of said DCRS1 and said DSRS1 proteins, thereby forming said receptor complex.

20. A method of screening for ligands for a receptor complex comprising said DCRS1 and said DSRS1 proteins, comprising screening a library of compounds for binding to said cell of Claim 17.

SEQUENCE SUBMISSION

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Lys Ser Glu Trp Ala Thr His Lys Phe Ala Asp Cys Lys Ala Lys Arg
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Asp Thr Pro Thr Ser Cys Thr Val Asp Tyr Ser Thr Val Tyr Phe Val
180 185 190

Asn Ile Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Thr
195 200 205

Ser Asp His Ile Asn Phe Asp Pro Val Tyr Lys Val Lys Pro Asn Pro
210 215 220

Pro His Asn Leu Ser Val Ile Asn Ser Glu Glu Leu Ser Ser Ile Leu
225 230 235 240

Lys Leu Thr Trp Thr Asn Pro Ser Ile Lys Ser Val Ile Ile Leu Lys
245 250 255

Tyr Asn Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ser Gln Ile
260 265 270

Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln Asp
275 280 285

Leu Lys Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Cys Met Lys Glu
290 295 300

Asp Gly Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Ile
305 310 315 320

Thr Tyr Glu Asp Arg Pro Ser Lys Ala Pro Ser Phe Trp Tyr Lys Ile
325 330 335

Asp Pro Ser His Thr Gln Gly Tyr Arg Thr Val Gln Leu Val Trp Lys
340 345 350

Thr Leu Pro Pro Phe Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val
355 360 365

Thr Leu Thr Arg Trp Lys Ser His Leu Gln Asn Tyr Thr Val Asn Ala
370 375 380

Thr Lys Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Leu Ala Thr Leu
385 390 395 400

Thr Val Arg Asn Leu Val Gly Lys Ser Asp Ala Ala Val Leu Thr Ile
405 410 415

Pro Ala Cys Asp Phe Gln Ala Thr His Pro Val Met Asp Leu Lys Ala
420 425 430

Phe Pro Lys Asp Asn Met Leu Trp Val Glu Trp Thr Thr Pro Arg Glu
435 440 445

Ser Val Lys Lys Tyr Ile Leu Glu Trp Cys Val Leu Ser Asp Lys Ala
450 455 460

Pro Cys Ile Thr Asp Trp Gln Gln Glu Asp Gly Thr Val His Arg Thr
465 470 475 480

Tyr Leu Arg Gly Asn Leu Ala Glu Ser Lys Cys Tyr Leu Ile Thr Val
485 490 495

Thr Pro Val Tyr Ala Asp Gly Pro Gly Ser Pro Glu Ser Ile Lys Ala
500 505 510

Tyr Leu Lys Gln Ala Pro Pro Ser Lys Gly Pro Thr Val Arg Thr Lys
515 520 525

Lys Val Gly Lys Asn Glu Ala Val Leu Glu Trp Asp Gln Leu Pro Val
530 535 540

Asp Val Gln Asn Gly Phe Ile Arg Asn Tyr Thr Ile Phe Tyr Arg Thr
545 550 555 560

Ile Ile Gly Asn Glu Thr Ala Val Asn Val Asp Ser Ser His Thr Glu
565 570 575

Tyr Thr Leu Ser Ser Leu Thr Ser Asp Thr Leu Tyr Met Val Arg Met
580 585 590

Ala Ala Tyr Thr Asp Glu Gly Gly Lys Asp Gly Pro Glu Phe Thr Phe
595 600 605

Thr Thr Pro Lys Phe Ala Gln Gly Glu Ile Glu Ala Ile Val Val Pro
610 615 620

Val Cys Leu Ala Phe Leu Leu Thr Thr Leu Leu Gly Val Leu Phe Cys
625 630 635 640

Phe Asn Lys Arg Asp Leu Ile Lys Lys His Ile Trp Pro Asn Val Pro
645 650 655

Asp Pro Ser Lys Ser His Ile Ala Gln Trp Ser Pro His Thr Pro Pro
660 665 670

Arg His Asn Phe Asn Ser Lys Asp Gln Met Tyr Ser Asp Gly Asn Phe
675 680 685

Thr Asp Val Ser Val Val Glu Ile Glu Ala Asn Asp Lys Lys Pro Phe
690 695 700

Pro Glu Asp Leu Lys Ser Leu Asp Leu Phe Lys Lys Glu Lys Ile Asn
705 710 715 720

Thr Glu Gly His Ser Ser Gly Ile Gly Gly Ser Ser Cys Met Ser Ser
725 730 735

Ser Arg Pro Ser Ile Ser Ser Ser Asp Glu Asn Glu Ser Ser Gln Asn
740 745 750

Thr Ser Ser Thr Val Gln Tyr Ser Thr Val Val His Ser Gly Tyr Arg
755 760 765

His Gln Val Pro Ser Val Gln Val Phe Ser Arg Ser Glu Ser Thr Gln
770 775 780

Pro Leu Leu Asp Ser Glu Glu Arg Pro Glu Asp Leu Gln Leu Val Asp
785 790 795 800

His Val Asp Gly Gly Asp Gly Ile Leu Pro Arg Gln Gln Tyr Phe Lys
805 810 815

Gln Asn Cys Ser Gln His Glu Ser Ser Pro Asp Ile Ser His Phe Glu
820 825 830

Arg Ser Lys Gln Val Ser Ser Val Asn Glu Glu Asp Phe Val Arg Leu
835 840 845

Lys Gln Gln Ile Ser Asp His Ile Ser Gln Ser Cys Gly Ser Gly Gln
850 855 860

Met Lys Met Phe Gln Glu Val Ser Ala Ala Asp Ala Phe Gly Pro Gly
865 870 875 880

Thr Glu Gly Gln Val Glu Arg Phe Glu Thr Val Gly Met Glu Ala Ala
885 890 895

Thr Asp Glu Gly Met Pro Lys Ser Tyr Leu Pro Gln Thr Val Arg Gln
900 905 910

Gly Gly Tyr Met Pro Gln
915

<210> 6
<211> 836
<212> PRT
<213> primate

<400> 6
Met Ala Arg Leu Gly Asn Cys Ser Leu Thr Trp Ala Ala Leu Ile Ile
1 5 10 15

Leu Leu Leu Pro Gly Ser Leu Glu Glu Cys Gly His Ile Ser Val Ser
20 25 30

Ala Pro Ile Val His Leu Gly Asp Pro Ile Thr Ala Ser Cys Ile Ile
35 40 45

Lys Gln Asn Cys Ser His Leu Asp Pro Glu Pro Gln Ile Leu Trp Arg
50 55 60

Leu Gly Ala Glu Leu Gln Pro Gly Gly Arg Gln Gln Arg Leu Ser Asp
65 70 75 80

Gly Thr Gln Glu Ser Ile Ile Thr Leu Pro His Leu Asn His Thr Gln
85 90 95

Ala Phe Leu Ser Cys Cys Leu Asn Trp Gly Asn Ser Leu Gln Ile Leu
100 105 110

Asp Gln Val Glu Leu Arg Ala Gly Tyr Pro Pro Ala Ile Pro His Asn
115 120 125

Leu Ser Cys Leu Met Asn Leu Thr Thr Ser Ser Leu Ile Cys Gln Trp
130 135 140

Glu Pro Gly Pro Glu Thr His Leu Pro Thr Ser Phe Thr Leu Lys Ser
145 150 155 160

Phe Lys Ser Arg Gly Asn Cys Gln Thr Gln Gly Asp Ser Ile Leu Asp
165 170 175

```
Cys Val Pro Lys Asp Gly Gln Ser His Cys Cys Ile Pro Arg Lys His
            180                 185                 190

Leu Leu Leu Tyr Gln Asn Met Gly Ile Trp Val Gln Ala Glu Asn Ala
        195                 200                 205

Leu Gly Thr Ser Met Ser Pro Gln Leu Cys Leu Asp Pro Met Asp Val
    210                 215                 220

Val Lys Leu Glu Pro Pro Met Leu Arg Thr Met Asp Pro Ser Pro Glu
225                 230                 235                 240

Ala Ala Pro Pro Gln Ala Gly Cys Leu Gln Leu Cys Trp Glu Pro Trp
                245                 250                 255

Gln Pro Gly Leu His Ile Asn Gln Lys Cys Glu Leu Arg His Lys Pro
            260                 265                 270

Gln Arg Gly Glu Ala Ser Trp Ala Leu Val Gly Pro Leu Pro Leu Glu
        275                 280                 285

Ala Leu Gln Tyr Glu Leu Cys Gly Leu Leu Pro Ala Thr Ala Tyr Thr
    290                 295                 300

Leu Gln Ile Arg Cys Ile Arg Trp Pro Leu Pro Gly His Trp Ser Asp
305                 310                 315                 320

Trp Ser Pro Ser Leu Glu Leu Arg Thr Thr Glu Arg Ala Pro Thr Val
                325                 330                 335

Arg Leu Asp Thr Trp Trp Arg Gln Arg Gln Leu Asp Pro Arg Thr Val
            340                 345                 350

Gln Leu Phe Trp Lys Pro Val Pro Leu Glu Glu Asp Ser Gly Arg Ile
        355                 360                 365

Gln Gly Tyr Val Val Ser Trp Arg Pro Ser Gly Gln Ala Gly Ala Ile
    370                 375                 380

Leu Pro Leu Cys Asn Thr Thr Glu Leu Ser Cys Thr Phe His Leu Pro
385                 390                 395                 400

Ser Glu Ala Gln Glu Val Ala Leu Val Ala Tyr Asn Ser Ala Gly Thr
                405                 410                 415

Ser Arg Pro Thr Pro Val Val Phe Ser Glu Ser Arg Gly Pro Ala Leu
            420                 425                 430

Thr Arg Leu His Ala Met Ala Arg Asp Pro His Ser Leu Trp Val Gly
        435                 440                 445

Trp Glu Pro Pro Asn Pro Trp Pro Gln Gly Tyr Val Ile Glu Trp Gly
    450                 455                 460

Leu Gly Pro Pro Ser Ala Ser Asn Ser Asn Lys Thr Trp Arg Met Glu
465                 470                 475                 480

Gln Asn Gly Arg Ala Thr Gly Phe Leu Leu Lys Glu Asn Ile Arg Pro
                485                 490                 495
```

```
Phe Gln Leu Tyr Glu Ile Ile Val Thr Pro Leu Tyr Gln Asp Thr Met
500                 505                 510

Gly Pro Ser Gln His Val Tyr Ala Tyr Ser Gln Glu Met Ala Pro Ser
515                 520                 525

His Ala Pro Glu Leu His Leu Lys His Ile Gly Lys Thr Trp Ala Gln
530                 535                 540

Leu Glu Trp Val Pro Glu Pro Pro Glu Leu Gly Lys Ser Pro Leu Thr
545                 550                 555                 560

His Tyr Thr Ile Phe Trp Thr Asn Ala Gln Asn Gln Ser Phe Ser Ala
                565                 570                 575

Ile Leu Asn Ala Ser Ser Arg Gly Phe Val Leu His Gly Leu Glu Pro
580                 585                 590

Ala Ser Leu Tyr His Ile His Leu Met Ala Ala Ser Gln Ala Gly Ala
595                 600                 605

Thr Asn Ser Thr Val Leu Thr Leu Met Thr Leu Thr Pro Glu Gly Ser
610                 615                 620

Glu Leu His Ile Ile Leu Gly Leu Phe Gly Leu Leu Leu Leu Leu Thr
625                 630                 635                 640

Cys Leu Cys Gly Thr Ala Trp Leu Cys Cys Ser Pro Asn Arg Lys Asn
                645                 650                 655

Pro Leu Trp Pro Ser Val Pro Asp Pro Ala His Ser Ser Leu Gly Ser
660                 665                 670

Trp Val Pro Thr Ile Met Glu Glu Asp Ala Phe Gln Leu Pro Gly Leu
675                 680                 685

Gly Thr Pro Pro Ile Thr Lys Leu Thr Val Leu Glu Glu Asp Glu Lys
690                 695                 700

Lys Pro Val Pro Trp Glu Ser His Asn Ser Ser Glu Thr Cys Gly Leu
705                 710                 715                 720

Pro Thr Leu Val Gln Thr Tyr Val Leu Gln Gly Asp Pro Arg Ala Val
                725                 730                 735

Ser Thr Gln Pro Gln Ser Gln Ser Gly Thr Ser Asp Gln Val Leu Tyr
740                 745                 750

Gly Gln Leu Leu Gly Ser Pro Thr Ser Pro Gly Pro Gly His Tyr Leu
755                 760                 765

Arg Cys Asp Ser Thr Gln Pro Leu Leu Ala Gly Leu Thr Pro Ser Pro
770                 775                 780

Lys Ser Tyr Glu Asn Leu Trp Phe Gln Ala Ser Pro Leu Gly Thr Leu
785                 790                 795                 800

Val Thr Pro Ala Pro Ser Gln Glu Asp Asp Cys Val Phe Gly Pro Leu
                805                 810                 815
```

Leu Asn Phe Pro Leu Leu Gln Gly Ile Arg Val His Gly Met Glu Ala
820 825 830

Leu Gly Ser Phe
835

<210> 7
<211> 862
<212> PRT
<213> primate

<400> 7
Met Ala His Thr Phe Arg Gly Cys Ser Leu Ala Phe Met Phe Ile Ile
1 5 10 15

Thr Trp Leu Leu Ile Lys Ala Lys Ile Asp Ala Cys Lys Arg Gly Asp
20 25 30

Val Thr Val Lys Pro Ser His Val Ile Leu Leu Gly Ser Thr Val Asn
35 40 45

Ile Thr Cys Ser Leu Lys Pro Arg Gln Gly Cys Phe His Tyr Ser Arg
50 55 60

Arg Asn Lys Leu Ile Leu Tyr Lys Phe Asp Arg Arg Ile Asn Phe His
65 70 75 80

His Gly His Ser Leu Asn Ser Gln Val Thr Gly Leu Pro Leu Gly Thr
85 90 95

Thr Leu Phe Val Cys Lys Leu Ala Cys Ile Asn Ser Asp Glu Ile Gln
100 105 110

Ile Cys Gly Ala Glu Ile Phe Val Gly Val Ala Pro Glu Gln Pro Gln
115 120 125

Asn Leu Ser Cys Ile Gln Lys Gly Glu Gln Gly Thr Val Ala Cys Thr
130 135 140

Trp Glu Arg Gly Arg Asp Thr His Leu Tyr Thr Glu Tyr Thr Leu Gln
145 150 155 160

Leu Ser Gly Pro Lys Asn Leu Thr Trp Gln Lys Gln Cys Lys Asp Ile
165 170 175

Tyr Cys Asp Tyr Leu Asp Phe Gly Ile Asn Leu Thr Pro Glu Ser Pro
180 185 190

Glu Ser Asn Phe Thr Ala Lys Val Thr Ala Val Asn Ser Leu Gly Ser
195 200 205

Ser Ser Ser Leu Pro Ser Thr Phe Thr Phe Leu Asp Ile Val Arg Pro
210 215 220

Leu Pro Pro Trp Asp Ile Arg Ile Lys Phe Gln Lys Ala Ser Val Ser
225 230 235 240

Arg Cys Thr Leu Tyr Trp Arg Asp Glu Gly Leu Val Leu Leu Asn Arg
245 250 255

```
Leu Arg Tyr Arg Pro Ser Asn Ser Arg Leu Trp Asn Met Val Asn Val
            260                 265                 270

Thr Lys Ala Lys Gly Arg His Asp Leu Leu Asp Leu Lys Pro Phe Thr
        275                 280                 285

Glu Tyr Glu Phe Gln Ile Ser Ser Lys Leu His Leu Tyr Lys Gly Ser
    290                 295                 300

Trp Ser Asp Trp Ser Glu Ser Leu Arg Ala Gln Thr Pro Glu Glu Glu
305                 310                 315                 320

Pro Thr Gly Met Leu Asp Val Trp Tyr Met Lys Arg His Ile Asp Tyr
                325                 330                 335

Ser Arg Gln Gln Ile Ser Leu Phe Trp Lys Asn Leu Ser Val Ser Glu
            340                 345                 350

Ala Arg Gly Lys Ile Leu His Tyr Gln Val Thr Leu Gln Glu Leu Thr
        355                 360                 365

Gly Gly Lys Ala Met Thr Gln Asn Ile Thr Gly His Thr Ser Trp Thr
    370                 375                 380

Thr Val Ile Pro Arg Thr Gly Asn Trp Ala Val Ala Val Ser Ala Ala
385                 390                 395                 400

Asn Ser Lys Gly Ser Ser Leu Pro Thr Arg Ile Asn Ile Met Asn Leu
                405                 410                 415

Cys Glu Ala Gly Leu Leu Ala Pro Arg Gln Val Ser Ala Asn Ser Glu
            420                 425                 430

Gly Met Asp Asn Ile Leu Val Thr Trp Gln Pro Pro Arg Lys Asp Pro
        435                 440                 445

Ser Ala Val Gln Glu Tyr Val Val Glu Trp Arg Glu Leu His Pro Gly
    450                 455                 460

Gly Asp Thr Gln Val Pro Leu Asn Trp Leu Arg Ser Arg Pro Tyr Asn
465                 470                 475                 480

Val Ser Ala Leu Ile Ser Glu Asn Ile Lys Ser Tyr Ile Cys Tyr Glu
                485                 490                 495

Ile Arg Val Tyr Ala Leu Ser Gly Asp Gln Gly Gly Cys Ser Ser Ile
            500                 505                 510

Leu Gly Asn Ser Lys His Lys Ala Pro Leu Ser Gly Pro His Ile Asn
        515                 520                 525

Ala Ile Thr Glu Glu Lys Gly Ser Ile Leu Ile Ser Trp Asn Ser Ile
    530                 535                 540

Pro Val Gln Glu Gln Met Gly Cys Leu Leu His Tyr Arg Ile Tyr Trp
545                 550                 555                 560

Lys Glu Arg Asp Ser Asn Ser Gln Pro Gln Leu Cys Glu Ile Pro Tyr
                565                 570                 575
```

Arg Val Ser Gln Asn Ser His Pro Ile Asn Ser Leu Gln Pro Arg Val
580 585 590

Thr Tyr Val Leu Trp Met Thr Ala Leu Thr Ala Ala Gly Glu Ser Ser
595 600 605

His Gly Asn Glu Arg Glu Phe Cys Leu Gln Gly Lys Ala Asn Trp Met
610 615 620

Ala Phe Val Ala Pro Ser Ile Cys Ile Ala Ile Ile Met Val Gly Ile
625 630 635 640

Phe Ser Thr His Tyr Phe Gln Gln Lys Val Phe Val Leu Leu Ala Ala
645 650 655

Leu Arg Pro Gln Trp Cys Ser Arg Glu Ile Pro Asp Pro Ala Asn Ser
660 665 670

Thr Cys Ala Lys Lys Tyr Pro Ile Ala Glu Glu Lys Thr Gln Leu Pro
675 680 685

Leu Asp Arg Leu Leu Ile Asp Trp Pro Thr Pro Glu Asp Pro Glu Pro
690 695 700

Leu Val Ile Ser Glu Val Leu His Gln Val Thr Pro Val Phe Arg His
705 710 715 720

Pro Pro Cys Ser Asn Trp Pro Gln Arg Glu Lys Gly Ile Gln Gly His
725 730 735

Gln Ala Ser Glu Lys Asp Met Met His Ser Ala Ser Ser Pro Pro Pro
740 745 750

Pro Arg Ala Leu Gln Ala Glu Ser Arg Gln Leu Val Asp Leu Tyr Lys
755 760 765

Val Leu Glu Ser Arg Gly Ser Asp Pro Lys Pro Glu Asn Pro Ala Cys
770 775 780

Pro Trp Thr Val Leu Pro Ala Gly Asp Leu Pro Thr His Asp Gly Tyr
785 790 795 800

Leu Pro Ser Asn Ile Asp Asp Leu Pro Ser His Glu Ala Pro Leu Ala
805 810 815

Asp Ser Leu Glu Glu Leu Glu Pro Gln His Ile Ser Leu Ser Val Phe
820 825 830

Pro Ser Ser Ser Leu His Pro Leu Thr Phe Ser Cys Gly Asp Lys Leu
835 840 845

Thr Leu Asp Gln Leu Lys Met Arg Cys Asp Ser Leu Met Leu
850 855 860

<210> 8
<211> 1233
<212> DNA
<213> primate

<220>
<221> CDS
<222> (1)..(1230)

<400> 8

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atg ccc gcc ggc cgc cgg ggc ccc gcc gcc caa tcc gcg cgg cgg ccg   48
Met Pro Ala Gly Arg Arg Gly Pro Ala Ala Gln Ser Ala Arg Arg Pro
  1               5                  10                  15

ccg ccg ttg ctg ccc ctg ctg ctg ctg ctc tgc gtc ctc ggg gcg ccg   96
Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Ala Pro
             20                  25                  30

cga gcc gga tca gga gcc cac aca gct gtg atc agt ccc cag gat ccc   144
Arg Ala Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro Gln Asp Pro
         35                  40                  45

acg ctt ctc atc ggc tcc tcc ctg ctg gcc acc tgc tca gtg cac gga   192
Thr Leu Leu Ile Gly Ser Ser Leu Leu Ala Thr Cys Ser Val His Gly
     50                  55                  60

gac cca cca gga gcc acc gcc gag ggc ctc tac tgg acc ctc aac ggg   240
Asp Pro Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly
 65                  70                  75                  80

cgc cgc ctg ccc cct gag ctc tcc cgt gta ctc aac gcc tcc acc ttg   288
Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn Ala Ser Thr Leu
                 85                  90                  95

gct ctg gcc ctg gcc aac ctc aat ggg tcc agg cag cgg tcg ggg gac   336
Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Arg Ser Gly Asp
            100                 105                 110

aac ctc gtg tgc cac gcc cgt gac ggc agc atc ctg gct ggc tcc tgc   384
Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys
        115                 120                 125

ctc tat gtt ggc ctg ccc cca gag aaa ccc gtc aac atc agc tgc tgg   432
Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn Ile Ser Cys Trp
    130                 135                 140

tcc aag aac atg aag gac ttg acc tgc cgc tgg acg cca ggg gcc cac   480
Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala His
145                 150                 155                 160

ggg gag acc ttc ctc cac acc aac tac tcc ctc aag tac aag ctt agg   528
Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg
                165                 170                 175

tgg tat ggc cag gac aac aca tgt gag gag tac cac aca gtg ggg ccc   576
Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly Pro
            180                 185                 190

cac tcc tgc cac atc ccc aag gac ctg gct ctc ttt acg ccc tat gag   624
His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu
        195                 200                 205

atc tgg gtg gag gcc acc aac cgc ctg ggc tct gcc cgc tcc gat gta   672
Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp Val
    210                 215                 220
```

```
ctc acg ctg gat atc ctg gat gtg gtg acc acg gac ccc ccg ccc gac   720
Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp Pro Pro Pro Asp
225                 230                 235                 240

gtg cac gtg agc cgc gtc ggg ggc ctg gag gac cag ctg agc gtg cgc   768
Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val Arg
                245                 250                 255

tgg gtg tcg cca ccc gcc ctc aag gat ttc ctc ttt caa gcc aaa tac   816
Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr
            260                 265                 270

cag atc cgc tac cga gtg gag gac agt gtg gac tgg aag gtg gtg gac   864
Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val Asp
        275                 280                 285

gat gtg agc aac cag acc tcc tgc cgc ctg gcc ggc ctg aaa ccc ggc   912
Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly
    290                 295                 300

acc gtg tac ttc gtg caa gtg cgc tgc aac ccc ttt ggc atc tat ggc   960
Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly
305                 310                 315                 320

tcc aag aaa gcc ggg atc tgg agt gag tgg agc cac ccc aca gcc gcc   1008
Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala Ala
                325                 330                 335

tcc act ccc cgc agt gag cgc ccg ggc ccg ggc ggc ggg gcg tgc gaa   1056
Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Ala Cys Glu
            340                 345                 350

ccg cgg ggc gga gag ccg agc tcg ggg ccg gtg cgg cgc gag ctc aag   1104
Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu Lys
        355                 360                 365

cag ttc ctg ggc tgg ctc aag aag cac gcg tac tgc tcc aac ctc agc   1152
Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu Ser
    370                 375                 380

ttc cgc ctc tac gac cag tgg cga gcc tgg atg cag aag tcg cac aag   1200
Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His Lys
385                 390                 395                 400

acc cgc aac cag gtc ctg cca gat aag ctg tag                      1233
Thr Arg Asn Gln Val Leu Pro Asp Lys Leu
                405                 410
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<210> 9
<211> 410
<212> PRT
<213> primate

<400> 9

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Met Pro Ala Gly Arg Arg Gly Pro Ala Ala Gln Ser Ala Arg Arg Pro
  1               5                  10                  15

Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Ala Pro
            20                  25                  30
```

```
Arg Ala Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro Gln Asp Pro
          35                  40                  45

Thr Leu Leu Ile Gly Ser Ser Leu Leu Ala Thr Cys Ser Val His Gly
     50                  55                  60

Asp Pro Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly
 65                  70                  75                  80

Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn Ala Ser Thr Leu
                 85                  90                  95

Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Arg Ser Gly Asp
            100                 105                 110

Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys
        115                 120                 125

Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn Ile Ser Cys Trp
    130                 135                 140

Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala His
145                 150                 155                 160

Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg
                165                 170                 175

Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly Pro
            180                 185                 190

His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu
        195                 200                 205

Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp Val
    210                 215                 220

Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp Pro Pro Pro Asp
225                 230                 235                 240

Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val Arg
                245                 250                 255

Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr
            260                 265                 270

Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val Asp
        275                 280                 285

Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly
    290                 295                 300

Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly
305                 310                 315                 320

Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala Ala
                325                 330                 335

Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Ala Cys Glu
            340                 345                 350
```

```
Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu Lys
        355                 360                 365

Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu Ser
    370                 375                 380

Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His Lys
385                 390                 395                 400

Thr Arg Asn Gln Val Leu Pro Asp Lys Leu
                405                 410
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<210> 10
<211> 1524
<212> DNA
<213> rodent

<220>
<221> CDS
<222> (1)..(1248)

<400> 10

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ccc tca cta aag gga ata agc ttg cgg ccg ctg tcc tcg ctg tgg tcg   48
Pro Ser Leu Lys Gly Ile Ser Leu Arg Pro Leu Ser Ser Leu Trp Ser
  1               5                  10                  15

cct ctg ttg ctc tgt gtc ctc ggg gtg cct cgg ggc gga tcg gga gcc   96
Pro Leu Leu Leu Cys Val Leu Gly Val Pro Arg Gly Gly Ser Gly Ala
             20                  25                  30

cac aca gct gta atc agc ccc cag gac ccc acc ctt ctc atc ggc tcc   144
His Thr Ala Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser
         35                  40                  45

tcc ctg caa gct acc tgc tct ata cat gga gac aca cct ggg gcc acc   192
Ser Leu Gln Ala Thr Cys Ser Ile His Gly Asp Thr Pro Gly Ala Thr
     50                  55                  60

gct gag ggg ctc tac tgg acc ctc aat ggt cgc cgc ctg ccc tct gag   240
Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly Arg Arg Leu Pro Ser Glu
 65                  70                  75                  80

ctg tcc cgc ctc ctt aac acc tcc acc ctg gcc ctg gcc ctg gct aac   288
Leu Ser Arg Leu Leu Asn Thr Ser Thr Leu Ala Leu Ala Leu Ala Asn
                 85                  90                  95

ctt aat ggg tcc agg cag cag tca gga gac aat ctg gtg tgt cac gcc   336
Leu Asn Gly Ser Arg Gln Gln Ser Gly Asp Asn Leu Val Cys His Ala
            100                 105                 110

cga gat ggc agc att ctg gct ggc tcc tgc ctc tat gtt ggc ttg ccc   384
Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro
        115                 120                 125

cct gag aag cct ttt aac atc agc tgc tgg tcc cgg aac atg aag gat   432
Pro Glu Lys Pro Phe Asn Ile Ser Cys Trp Ser Arg Asn Met Lys Asp
    130                 135                 140
```

```
ctc acg tgc cgc tgg aca ccg ggt gca cac ggg gag aca ttc tta cat   480
Leu Thr Cys Arg Trp Thr Pro Gly Ala His Gly Glu Thr Phe Leu His
145                 150                 155                 160

acc aac tac tcc ctc aag tac aag ctg agg tgg tac ggt cag gat aac   528
Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn
                165                 170                 175

aca tgt gag gag tac cac act gtg ggc cct cac tca tgc cat atc ccc   576
Thr Cys Glu Glu Tyr His Thr Val Gly Pro His Ser Cys His Ile Pro
            180                 185                 190

aag gac ctg gcc ctc ttc act ccc tat gag atc tgg gtg gaa gcc acc   624
Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr
        195                 200                 205

aat cgc cta ggc tca gca aga tct gat gtc ctc aca ctg gat gtc ctg   672
Asn Arg Leu Gly Ser Ala Arg Ser Asp Val Leu Thr Leu Asp Val Leu
    210                 215                 220

gac gtg gtg acc acg gac ccc cca ccc gac gtg cac gtg agc cgc gtt   720
Asp Val Val Thr Thr Asp Pro Pro Pro Asp Val His Val Ser Arg Val
225                 230                 235                 240

ggg ggc ctg gag gac cag ctg agt gtg cgc tgg gtc tca cca cca gct   768
Gly Gly Leu Glu Asp Gln Leu Ser Val Arg Trp Val Ser Pro Pro Ala
                245                 250                 255

ctc aag gat ttc ctc ttc caa gcc aag tac cag atc cgc tac cgc gtg   816
Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val
            260                 265                 270

gag gac agc gtg gac tgg aag gtg gtg gat gac gtc agc aac cag acc   864
Glu Asp Ser Val Asp Trp Lys Val Val Asp Asp Val Ser Asn Gln Thr
        275                 280                 285

tcc tgc cgt ctc gcg ggc ctg aag ccc ggc acc gtt tac ttc gtc caa   912
Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly Thr Val Tyr Phe Val Gln
    290                 295                 300

gtg cgt tgt aac cca ttc ggg atc tat ggg tcg aaa aag gcg gga atc   960
Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile
305                 310                 315                 320

tgg agc gag tgg agc cac ccc acc gct gcc tcc acc cct cga agt gag   1008
Trp Ser Glu Trp Ser His Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu
                325                 330                 335

cgc ccg ggc ccg ggc ggc ggg gtg tgc gag ccg cgg ggc ggc gag ccc   1056
Arg Pro Gly Pro Gly Gly Gly Val Cys Glu Pro Arg Gly Gly Glu Pro
            340                 345                 350

agc tcg ggc ccg gtg cgg cgc gag ctc aag cag ttc ctc ggc tgg ctc   1104
Ser Ser Gly Pro Val Arg Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu
        355                 360                 365

aag aag cac gca tac tgc tcg aac ctt agt ttc cgc ctg tac gac cag   1152
Lys Lys His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln
    370                 375                 380
```

tgg cgt gct tgg atg cag aag tca cac aag acc cga aac cag gac gag 1200
Trp Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln Asp Glu
385 390 395 400

ggg atc ctg ccc tcg ggc aga cgg ggt gcg gcg aga ggt cct gcc ggc 1248
Gly Ile Leu Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly
405 410 415

taaactctaa ggataggcca tcctcctgct gggtcagacc tggaggctca cctgaattgg 1308

agcccctctg taccatctgg gcaacaaaga aacctaccag aggctggggc acaatgagct 1368

cccacaacca cagctttggt ccacatgatg gtcacacttg gatatacccc agtgtgggta 1428

gggttggggt attgcagggc ctcccaagag ttttttaaa taaataaagg agttgttcag 1488

gtcccgatgg naaaaaaaaa aaaaaaaaaa aaaaaa 1524

<210> 11
<211> 416
<212> PRT
<213> rodent

<400> 11
Pro Ser Leu Lys Gly Ile Ser Leu Arg Pro Leu Ser Ser Leu Trp Ser
1 5 10 15

Pro Leu Leu Leu Cys Val Leu Gly Val Pro Arg Gly Gly Ser Gly Ala
20 25 30

His Thr Ala Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser
35 40 45

Ser Leu Gln Ala Thr Cys Ser Ile His Gly Asp Thr Pro Gly Ala Thr
50 55 60

Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly Arg Arg Leu Pro Ser Glu
65 70 75 80

Leu Ser Arg Leu Leu Asn Thr Ser Thr Leu Ala Leu Ala Leu Ala Asn
85 90 95

Leu Asn Gly Ser Arg Gln Gln Ser Gly Asp Asn Leu Val Cys His Ala
100 105 110

Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro
115 120 125

Pro Glu Lys Pro Phe Asn Ile Ser Cys Trp Ser Arg Asn Met Lys Asp
130 135 140

Leu Thr Cys Arg Trp Thr Pro Gly Ala His Gly Glu Thr Phe Leu His
145 150 155 160

Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn
165 170 175

Thr Cys Glu Glu Tyr His Thr Val Gly Pro His Ser Cys His Ile Pro
180 185 190

```
Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr
        195                 200                 205

Asn Arg Leu Gly Ser Ala Arg Ser Asp Val Leu Thr Leu Asp Val Leu
    210                 215                 220

Asp Val Val Thr Thr Asp Pro Pro Pro Asp Val His Val Ser Arg Val
225                 230                 235                 240

Gly Gly Leu Glu Asp Gln Leu Ser Val Arg Trp Val Ser Pro Pro Ala
                245                 250                 255

Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val
            260                 265                 270

Glu Asp Ser Val Asp Trp Lys Val Val Asp Asp Val Ser Asn Gln Thr
        275                 280                 285

Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly Thr Val Tyr Phe Val Gln
    290                 295                 300

Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile
305                 310                 315                 320

Trp Ser Glu Trp Ser His Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu
                325                 330                 335

Arg Pro Gly Pro Gly Gly Gly Val Cys Glu Pro Arg Gly Gly Glu Pro
            340                 345                 350

Ser Ser Gly Pro Val Arg Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu
        355                 360                 365

Lys Lys His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln
    370                 375                 380

Trp Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln Asp Glu
385                 390                 395                 400

Gly Ile Leu Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly
                405                 410                 415
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<210> 12
<211> 1911
<212> DNA
<213> primate

<220>
<221> CDS
<222> (1)..(1908)

<400> 12

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atg cgg gga ggc agg ggc gcc cct ttc tgg ctg tgg ccg ctg ccc aag   48
Met Arg Gly Gly Arg Gly Ala Pro Phe Trp Leu Trp Pro Leu Pro Lys
  1               5                  10                  15

ctg gcg ctg ctg cct ctg ttg tgg gtg ctt ttc cag cgg acg cgt ccc   96
Leu Ala Leu Leu Pro Leu Leu Trp Val Leu Phe Gln Arg Thr Arg Pro
            20                  25                  30
```

```
cag ggc agc gcc ggg cca ctg cag tgc tac gga gtt gga ccc ttg ggc   144
Gln Gly Ser Ala Gly Pro Leu Gln Cys Tyr Gly Val Gly Pro Leu Gly
          35                  40                  45

gac ttg aac tgc tcg tgg gag cct ctt ggg gac ctg gga gcc ccc tcc   192
Asp Leu Asn Cys Ser Trp Glu Pro Leu Gly Asp Leu Gly Ala Pro Ser
     50                  55                  60

gag tta cac ctc cag agc caa aag tac cgt tcc aac aaa acc cag act   240
Glu Leu His Leu Gln Ser Gln Lys Tyr Arg Ser Asn Lys Thr Gln Thr
 65                  70                  75                  80

gtg gca gtg gca gcc gga cgg agc tgg gtg gcc att cct cgg gaa cag   288
Val Ala Val Ala Ala Gly Arg Ser Trp Val Ala Ile Pro Arg Glu Gln
                 85                  90                  95

ctc acc atg tct gac aaa ctc ctt gtc tgg ggc ayt aag gca ggc cag   336
Leu Thr Met Ser Asp Lys Leu Leu Val Trp Gly Xaa Lys Ala Gly Gln
            100                 105                 110

cct ctc tgg ccc ccc gtc ttc gtg aac cta gaa acc caa atg aag cca   384
Pro Leu Trp Pro Pro Val Phe Val Asn Leu Glu Thr Gln Met Lys Pro
        115                 120                 125

aac gcc ccc cgg ctg ggc cct gac gtg gac ttt tcc gag gat gac ccc   432
Asn Ala Pro Arg Leu Gly Pro Asp Val Asp Phe Ser Glu Asp Asp Pro
    130                 135                 140

ctg gag gcc act gtc cat tgg gcc cca cct aca tgg cca tct cat aaa   480
Leu Glu Ala Thr Val His Trp Ala Pro Pro Thr Trp Pro Ser His Lys
145                 150                 155                 160

gtt ctg atc tgc cag ttc cac tac cga aga tgt cag gag gcg gcc tgg   528
Val Leu Ile Cys Gln Phe His Tyr Arg Arg Cys Gln Glu Ala Ala Trp
                165                 170                 175

acc ctg ctg gaa ccg gag ctg aag acc ata ccc ctg acc cct gtt gag   576
Thr Leu Leu Glu Pro Glu Leu Lys Thr Ile Pro Leu Thr Pro Val Glu
            180                 185                 190

atc caa gat ttg gag cta gcc act ggc tac aaa gtg tat ggc cgc tgc   624
Ile Gln Asp Leu Glu Leu Ala Thr Gly Tyr Lys Val Tyr Gly Arg Cys
        195                 200                 205

cgg atg gag aaa gaa gag gat ttg tgg ggc gag tgg agc ccc att ttg   672
Arg Met Glu Lys Glu Glu Asp Leu Trp Gly Glu Trp Ser Pro Ile Leu
    210                 215                 220

tcc ttc cag aca ccg cct tct gct cca aaa gat gtg tgg gta tca ggg   720
Ser Phe Gln Thr Pro Pro Ser Ala Pro Lys Asp Val Trp Val Ser Gly
225                 230                 235                 240

aac ctc tgt ggg acg cct gga gga gag gaa cct ttg ctt cta tgg aag   768
Asn Leu Cys Gly Thr Pro Gly Gly Glu Glu Pro Leu Leu Leu Trp Lys
                245                 250                 255

gcc cca ggg ccc tgt gtg cag gtg agc tac aaa gtc tgg ttc tgg gtt   816
Ala Pro Gly Pro Cys Val Gln Val Ser Tyr Lys Val Trp Phe Trp Val
            260                 265                 270
```

```
gga ggt cgt gag ctg agt cca gaa gga att acc tgc tgc tgc tcc cta   864
Gly Gly Arg Glu Leu Ser Pro Glu Gly Ile Thr Cys Cys Cys Ser Leu
        275                 280                 285

att ccc agt ggg gcg gag tgg gcc agg gtg tcc gct gtc aac gcc aca   912
Ile Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr
    290                 295                 300

agc tgg gag cct ctc acc aac ctc tct ttg gtc tgc ttg gat tca gcc   960
Ser Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala
305                 310                 315                 320

tct gcc ccc cgt agc gtg gca gtc agc agc atc gct ggg agc acg gag   1008
Ser Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu
                325                 330                 335

cta ctg gtg acc tgg caa ccg ggg cct ggg gaa cca ctg gag cat gta   1056
Leu Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val
            340                 345                 350

atg gac tgg gct cga gat ggg gac ccc ctg gag aaa ctc aac tgg gtc   1104
Met Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val
        355                 360                 365

cgg ctt ccc cct ggg aac ctc agt gct ctg tta cca ggg aat ttc act   1152
Arg Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr
    370                 375                 380

gtc ggg gtc ccc tat cga atc act gtg acc gca gtc tct gct tca ggc   1200
Val Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly
385                 390                 395                 400

ttg gcc tct gca tcc tcc gtc tgg ggg ttc agg gag gaa tta gca ccc   1248
Leu Ala Ser Ala Ser Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro
                405                 410                 415

cta gtg ggg cca acg ctt tgg cga ctc caa gat gcc cct cca ggg acc   1296
Leu Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr
            420                 425                 430

ccc gcc ata gcg tgg gga gag gtc cca agg cac cag ctt cga ggc cac   1344
Pro Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His
        435                 440                 445

ctc acc cac tac acc ttg tgt gca cag agt gga acc agc ccc tcc gtc   1392
Leu Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val
    450                 455                 460

tgc atg aat gtg agt ggc aac aca cag agt gtc acc ctg cct gac ctt   1440
Cys Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu
465                 470                 475                 480

cct tgg ggt ccc tgt gag ctg tgg gtg aca gca tct acc atc gct gga   1488
Pro Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly
                485                 490                 495

cag ggc cct cct ggt ccc atc ctc cgg ctt cat cta cca gat aac acc   1536
Gln Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr
            500                 505                 510
```

```
ctg agg tgg aaa gtt ctg ccg ggc atc cta ttc ttg tgg ggc ttg ttc   1584
Leu Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe
        515                 520                 525

ctg ttg ggg tgt ggc ctg agc ctg gcc acc tct gga agg tgc tac cac   1632
Leu Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His
    530                 535                 540

cta agg cac aaa gtg ctg ccc cgc tgg gtc tgg gag aaa gtt cct gat   1680
Leu Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp
545                 550                 555                 560

cct gcc aac agc agt tca ggc cag ccc cac atg gag caa gta cct gag   1728
Pro Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu
                565                 570                 575

gcc cag ccc ctt ggg gac ttg ccc atc ctg gaa gtg gag gag atg gag   1776
Ala Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu
            580                 585                 590

ccc ccg ccg gtt atg gag tcc tcc cag ccc gcc cag gcc acc gcc ccg   1824
Pro Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro
        595                 600                 605

ctt gac tct ggg tat gag aag cac ttc ctg ccc aca cct gag gag ctg   1872
Leu Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu
    610                 615                 620

ggc ctt ctg ggg ccc ccc agg cca cag gtt ctg gcc tga               1911
Gly Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala
625                 630                 635
```

<210> 13
<211> 636
<212> PRT
<213> primate

<400> 13

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Met Arg Gly Gly Arg Gly Ala Pro Phe Trp Leu Trp Pro Leu Pro Lys
  1               5                  10                  15

Leu Ala Leu Leu Pro Leu Leu Trp Val Leu Phe Gln Arg Thr Arg Pro
             20                  25                  30

Gln Gly Ser Ala Gly Pro Leu Gln Cys Tyr Gly Val Gly Pro Leu Gly
         35                  40                  45

Asp Leu Asn Cys Ser Trp Glu Pro Leu Gly Asp Leu Gly Ala Pro Ser
     50                  55                  60

Glu Leu His Leu Gln Ser Gln Lys Tyr Arg Ser Asn Lys Thr Gln Thr
 65                  70                  75                  80

Val Ala Val Ala Ala Gly Arg Ser Trp Val Ala Ile Pro Arg Glu Gln
                 85                  90                  95

Leu Thr Met Ser Asp Lys Leu Leu Val Trp Gly Xaa Lys Ala Gly Gln
            100                 105                 110
```

```
Pro Leu Trp Pro Pro Val Phe Val Asn Leu Glu Thr Gln Met Lys Pro
        115                 120                 125

Asn Ala Pro Arg Leu Gly Pro Asp Val Asp Phe Ser Glu Asp Asp Pro
    130                 135                 140

Leu Glu Ala Thr Val His Trp Ala Pro Pro Thr Trp Pro Ser His Lys
145                 150                 155                 160

Val Leu Ile Cys Gln Phe His Tyr Arg Arg Cys Gln Glu Ala Ala Trp
                165                 170                 175

Thr Leu Leu Glu Pro Glu Leu Lys Thr Ile Pro Leu Thr Pro Val Glu
            180                 185                 190

Ile Gln Asp Leu Glu Leu Ala Thr Gly Tyr Lys Val Tyr Gly Arg Cys
        195                 200                 205

Arg Met Glu Lys Glu Glu Asp Leu Trp Gly Glu Trp Ser Pro Ile Leu
    210                 215                 220

Ser Phe Gln Thr Pro Pro Ser Ala Pro Lys Asp Val Trp Val Ser Gly
225                 230                 235                 240

Asn Leu Cys Gly Thr Pro Gly Gly Glu Glu Pro Leu Leu Leu Trp Lys
                245                 250                 255

Ala Pro Gly Pro Cys Val Gln Val Ser Tyr Lys Val Trp Phe Trp Val
            260                 265                 270

Gly Gly Arg Glu Leu Ser Pro Glu Gly Ile Thr Cys Cys Cys Ser Leu
        275                 280                 285

Ile Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr
    290                 295                 300

Ser Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala
305                 310                 315                 320

Ser Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu
                325                 330                 335

Leu Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val
            340                 345                 350

Met Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val
        355                 360                 365

Arg Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr
    370                 375                 380

Val Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly
385                 390                 395                 400

Leu Ala Ser Ala Ser Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro
                405                 410                 415

Leu Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr
            420                 425                 430
```

Pro Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His
435 440 445

Leu Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val
450 455 460

Cys Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu
465 470 475 480

Pro Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly
485 490 495

Gln Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr
500 505 510

Leu Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe
515 520 525

Leu Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His
530 535 540

Leu Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp
545 550 555 560

Pro Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu
565 570 575

Ala Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu
580 585 590

Pro Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro
595 600 605

Leu Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu
610 615 620

Gly Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala
625 630 635

<210> 14
<211> 450
<212> DNA
<213> rodent

<220>
<221> CDS
<222> (1)..(450)

<400> 14
ggt aag ccc caa gcc tgg tgg tgt cac ttg tcc ctg gga gcc atg aac 48
Gly Lys Pro Gln Ala Trp Trp Cys His Leu Ser Leu Gly Ala Met Asn
1 5 10 15

cgg ctc ggg ttt gca cgc ctc acg ccg ttg gag ctt ctg ctg tcg ctg 96
Arg Leu Gly Phe Ala Arg Leu Thr Pro Leu Glu Leu Leu Leu Ser Leu
20 25 30

```
atg tcg ctg ctg ctc ggg acg cgg ccc cac ggc agt cca ggc cca ctg   144
Met Ser Leu Leu Leu Gly Thr Arg Pro His Gly Ser Pro Gly Pro Leu
          35                  40                  45

cag tgc tac agc gtc ggt ccc ctg gga atc ctg aac tgc tcc tgg gaa   192
Gln Cys Tyr Ser Val Gly Pro Leu Gly Ile Leu Asn Cys Ser Trp Glu
     50                  55                  60

cct ttg ggc gac ctg gag act cca cct gtg ctg tat cac cag agt cag   240
Pro Leu Gly Asp Leu Glu Thr Pro Pro Val Leu Tyr His Gln Ser Gln
 65                  70                  75                  80

aaa tac cat ccc aat aga gtc tgg gag gtg aag gtg cct tcc aaa cag   288
Lys Tyr His Pro Asn Arg Val Trp Glu Val Lys Val Pro Ser Lys Gln
                 85                  90                  95

agt tgg gtg acc att ccc cgg gaa cag ttc acc atg gct gac aaa ctc   336
Ser Trp Val Thr Ile Pro Arg Glu Gln Phe Thr Met Ala Asp Lys Leu
            100                 105                 110

ctc atc tgg ggg aca caa aag gga cgg cct ctg tgg tcc tct gtc tct   384
Leu Ile Trp Gly Thr Gln Lys Gly Arg Pro Leu Trp Ser Ser Val Ser
        115                 120                 125

gtg aac ctg gag acc caa atg aag cca gac aca cct cag atc ttc tct   432
Val Asn Leu Glu Thr Gln Met Lys Pro Asp Thr Pro Gln Ile Phe Ser
    130                 135                 140

caa gtg gat att tct gan                                          450
Gln Val Asp Ile Ser Xaa
145                 150
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<210> 15
<211> 150
<212> PRT
<213> rodent

<400> 15

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Gly Lys Pro Gln Ala Trp Trp Cys His Leu Ser Leu Gly Ala Met Asn
  1               5                  10                  15

Arg Leu Gly Phe Ala Arg Leu Thr Pro Leu Glu Leu Leu Leu Ser Leu
             20                  25                  30

Met Ser Leu Leu Leu Gly Thr Arg Pro His Gly Ser Pro Gly Pro Leu
          35                  40                  45

Gln Cys Tyr Ser Val Gly Pro Leu Gly Ile Leu Asn Cys Ser Trp Glu
     50                  55                  60

Pro Leu Gly Asp Leu Glu Thr Pro Pro Val Leu Tyr His Gln Ser Gln
 65                  70                  75                  80

Lys Tyr His Pro Asn Arg Val Trp Glu Val Lys Val Pro Ser Lys Gln
                 85                  90                  95

Ser Trp Val Thr Ile Pro Arg Glu Gln Phe Thr Met Ala Asp Lys Leu
            100                 105                 110
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Leu Ile Trp Gly Thr Gln Lys Gly Arg Pro Leu Trp Ser Ser Val Ser
115 120 125

Val Asn Leu Glu Thr Gln Met Lys Pro Asp Thr Pro Gln Ile Phe Ser
130 135 140

Gln Val Asp Ile Ser Xaa
145 150

<210> 16
<211> 570
<212> DNA
<213> primate

<220>
<221> CDS
<222> (1)..(567)

<220>
<221> mat_peptide
<222> (64)..(567)

<400> 16
atg ctg ggg agc aga gct gta atg ctg ctg ttg ctg ctg ccc tgg aca 48
Met Leu Gly Ser Arg Ala Val Met Leu Leu Leu Leu Pro Trp Thr
-20 -15 -10

gct cag ggc aga gct gtg cct ggg ggc agc agc cct gcc tgg act cag 96
Ala Gln Gly Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln
-5 -1 1 5 10

tgc cag cag ctt tca cag aag ctc tgc aca ctg gcc tgg agt gca cat 144
Cys Gln Gln Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His
15 20 25

cca cta gtg gga cac atg gat cta aga gaa gag gga gat gaa gag act 192
Pro Leu Val Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr
30 35 40

aca aat gat gtt ccc cat atc cag tgt gga gat ggc tgt gac ccc caa 240
Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln
45 50 55

gga ctc agg gac aac agt cag ttc tgc ttg caa agg atc cac cag ggt 288
Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly
60 65 70 75

ctg att ttt tat gag aag ctg cta gga tcg gat att ttc aca ggg gag 336
Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu
80 85 90

cct tct ctg ctc cct gat agc cct gtg gcg cag ctt cat gcc tcc cta 384
Pro Ser Leu Leu Pro Asp Ser Pro Val Ala Gln Leu His Ala Ser Leu
95 100 105

ctg ggc ctc agc caa ctc ctg cag cct gag ggt cac cac tgg gag act 432
Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
110 115 120

cag cag att cca agc ctc agt ccc agc cag cca tgg cag cgt ctc ctt 480
Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu
125 130 135

ctc cgc ttc aaa atc ctt cgc agc ctc cag gcc ttt gtg gct gta gcc 528
Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala
140 145 150 155

gcc cgg gtc ttt gcc cat gga gca gca acc ctg agt ccc taa 570
Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro
160 165

<210> 17
<211> 189
<212> PRT
<213> primate

<400> 17
Met Leu Gly Ser Arg Ala Val Met Leu Leu Leu Leu Leu Pro Trp Thr
-20 -15 -10

Ala Gln Gly Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln
-5 -1 1 5 10

Cys Gln Gln Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His
15 20 25

Pro Leu Val Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr
30 35 40

Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln
45 50 55

Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly
60 65 70 75

Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu
80 85 90

Pro Ser Leu Leu Pro Asp Ser Pro Val Ala Gln Leu His Ala Ser Leu
95 100 105

Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
110 115 120

Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu
125 130 135

Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala
140 145 150 155

Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro
160 165

<210> 18
<211> 1203
<212> DNA
<213> rodent

<220>
<221> CDS
<222> (113)..(700)

<220>
<221> mat_peptide
<222> (176)..(700)

<400> 18
cgcttagaag tcggactaca gagttagact cagaaccaaa ggaggtggat agggggtcca 60

caggcctggt gcagatcaca gagccagcca gatctgagaa gcagggaaca ag atg ctg 118
Met Leu
-20

gat tgc aga gca gta ata atg cta tgg ctg ttg ccc tgg gtc act cag 166
Asp Cys Arg Ala Val Ile Met Leu Trp Leu Leu Pro Trp Val Thr Gln
-15 -10 -5

ggc ctg gct gtg cct agg agt agc agt cct gac tgg gct cag tgc cag 214
Gly Leu Ala Val Pro Arg Ser Ser Ser Pro Asp Trp Ala Gln Cys Gln
-1 1 5 10

cag ctc tct cgg aat ctc tgc atg cta gcc tgg aac gca cat gca cca 262
Gln Leu Ser Arg Asn Leu Cys Met Leu Ala Trp Asn Ala His Ala Pro
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Cys Gln Gln Leu Ser Arg Asn Leu Cys Met Leu Ala Trp Asn Ala His
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Thr Lys Asn Asn Val Pro Arg Ile Gln Cys Glu Asp Gly Cys Asp Pro
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Gln Gly Leu Lys Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile Arg Gln
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Gly Leu Ala Phe Tyr Lys His Leu Leu Asp Ser Asp Ile Phe Lys Gly
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Glu Pro Ala Leu Leu Pro Asp Ser Pro Met Glu Gln Leu His Thr Ser
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Gln Pro Glu Gly His His Trp Glu Thr Glu Gln Thr Pro Ser Pro Ser
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Pro Ser Gln Pro Trp Gln Arg Leu Leu Leu Arg Leu Lys Ile Leu Arg
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Ser Leu Gln Ala Phe Val Ala Val Ala Ala Arg Val Phe Ala His Gly
85 90 95

Ala Ala Thr Leu Ser Gln
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/715 C07K14/54 C07K16/24 C07K16/28
G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 44455 A (ZYMOGENETICS INC) 27 November 1997 (1997-11-27) compare SEQ ID NO:5 with SEQ ID NO:13 in the present application page 3, line 12 - line 17	1-6, 11-20
A	FISCHER M ET AL: "A BIOACTIVE DESIGNER CYTOKINE FOR HUMAN HEMATOPOIETIC PROGENITOR CELL EXPANSION" NATURE BIOTECHNOLOGY, vol. 15, no. 2, 1 February 1997 (1997-02-01), pages 142-145, XP002047603 ISSN: 1087-0156 page 144, last paragraph; figure 1	1-6, 11-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1999	20/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cupido, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/US 99/02600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 05280 A (SCHERING CORPORATION; BAZAN JF) 4 February 1999 (1999-02-04) compare SEQ ID NO:2 with SEQ ID NO:17 in this application	1-6, 11-20
P,A	WO 98 31811 A (DONALDSON DEBRA D ;GENETICS INST (US); COLLINS MARY (US); NEBEN TA) 23 July 1998 (1998-07-23) compare amino acid residues 18-425 in SEQ ID NO:5 with residues 9-416 in SEQ ID NO:11of the present application	1-6, 11-20
P,A	WO 98 49307 A (ZYMOGENETICS INC) 5 November 1998 (1998-11-05) compare SEQ ID NO:2 with SEQ ID NO:9 of the present application	1-6, 11-20
P,A	WO 98 11225 A (NICOLA NICOS ANTONY ;FABRI LOUIS (AU); FARLEY ALISON (AU); NASH AN) 19 March 1998 (1998-03-19) compare SEQ ID NO:13 with SEQ ID NO:9 in the present application	1-6, 11-20

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/02600

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-11

The claimed epitope is disclosed in a manner that does not allow a meaningful search

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 99/02600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9744455 A	27-11-1997	US 5792850 A	11-08-1998
		AU 3009397 A	09-12-1997
		EP 0910635 A	28-04-1999
WO 9905280 A	04-02-1999	AU 8589498 A	16-02-1999
WO 9831811 A	23-07-1998	AU 5733898 A	07-08-1998
WO 9849307 A	05-11-1998	AU 7276098 A	24-11-1998
WO 9811225 A	19-03-1998	AU 4308097 A	02-04-1998